FORMULATION, DEVELOPMENT AND EVALUATION OF FLOATING-PULSATILE DRUG DELIVERY SYSTEM OF NIFEDIPINE

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IN

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Submitted

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CERTIFICATE

This is to certify that this dissertation thesis entitled "**FORMULATION, DEVELOPMENT AND EVALUATION OF FLOATING PULSATILE DRUG DELIVERY SYSTEM OF NIFEDIPINE"** is a bonafide genuine research work carried out by **Mr. Sudarshan Vikas Borole (Reg. No. 26106303)** in Partial fulfillment of the requirements for the award of degree in **Master of Pharmacy in Pharmaceutics,** of **The Tamilnadu Dr. M.G.R. Medical University, Chennai**, in the Research and Development Centre, **JCPL Pharma (P) Ltd,Jalgaon** under my guidance and supervision to my fullest satisfaction.

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DECLARATION BY CANDIDATE

It gives me great pleasure and satisfaction to declare that the dissertation entitled "**FORMULATION, DEVELOPMENT AND EVALUATION OF FLOATING PULSATILE DRUG DELIVERY SYSTEM OF NIFEDIPINE"** is a bonafide genuine research work carried out by me in the JCPL Pharma (P) Ltd,Jalgaon under the guidance **of Dr.S.Umadevi** (Institutional Guide) Professor and head, Dept. of Pharmaceutics, R.V.S College of Pharmaceutical Sciences, Sulur, Coimbatore and **Mr. Ajay Barhate,** (Industrial Guide) Sr. Reaserch scientist of JCPL Pharma (P) Ltd,Jalgaon

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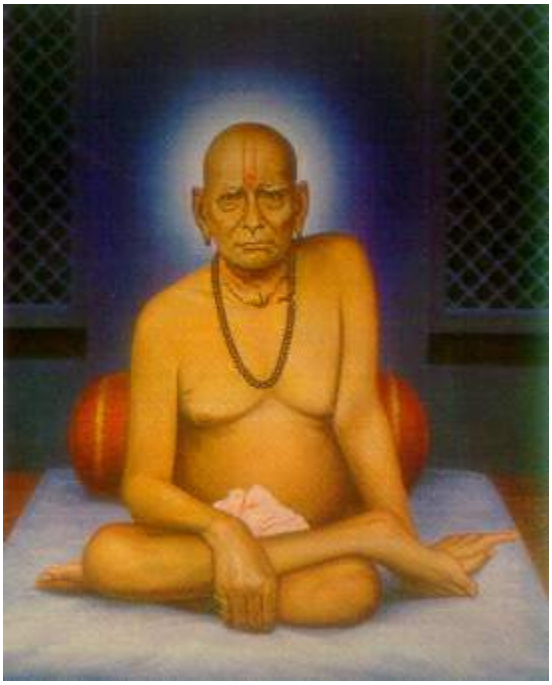
Dedicated to Almighty God

Shree Swami Samarth



&

My Beloved Parents

Whose love and affection are infinite

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LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
BCS	Biopharmaceutical Classification System
BP	British pharmacopoeia
Cmax	Maximum Plasma Concentration
CCS	Croscarmelose sodium
ChrDDS	chronopharmaceutical drug delivery systems
CR	Controlled Release
Camp	Cyclic adenocine mono phosphate
ECG	Electro-cardio gram
FPRT	Floating and pulsatile release tablet
GIT	Gastro intestinal tract
HA	Hyaluronic acid
HDPE	High-Density Polyethylene
HPMC	Hydroxypropylmethyl cellulose
ICH	International Conference on Harmonization
IR	Immediate Release
LDPE	Low Density Polyethylene
LOD	Loss On Drying
NaCl	Sodium Chloride
NaCMC	Carboxymethyl cellulose sodium
NSAIDs	Non-steroidal anti inflammatory drugs
PCT	Press-coated tablet.
PIPAAM	Poly (N-isopropylacrylamide)
PRT	Pulsatile release tablet
RRT	Rapid release tablet
Rpm	Revolution Per Minute
RES	Reticuloendothelial system
SI	Swelling index
TCES	time-controlled explosion system
t-max	Time to achieve Peak Plasma Concentration
USP	The United States Pharmacopoeia
USP NF	United State National Formulary

LIST OF TABLES

1. INTRODUCTION

1.1. CHRONOPHARMACEUTICS AND CHRONOTHERAPY [1-3]

The goal in drug delivery research is to develop formulations that meet therapeutic needs relating to particular pathological conditions. Up to late 1980`s design of drug delivery systems governed by the homeostatic theory. This theory is based on the assumption of biological functions that display constancy over time. Research in chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy. Optimal clinical outcome cannot be achieved if drug plasma concentrations are constant. If symptoms of disease display circadian variations drug release should also vary over time. Formulations should be justified by biopharmaceutical and pharmacokinetic study in order to choose the best hour for administration. Another point raised by circadian variation of physiological function is that drug pharmacokinetics can be time-dependent. Variations in physiological and pathophysiological functions in time, also need for variations of drug plasma concentration has brought a new approach to the development of drug delivery systems, chronopharmaceutical drug delivery.

The human body has many built-in rhythms known as biological clocks. Broadly, these can be classified as Ultradian, Circadian, Infradian and Seasonal. Ultradian cycles are shorter than a day, e.g. time taken for a nerve impulse to be transmitted. Circadian cycles last about 24 hours, e.g. sleeping and waking patterns. Infradian cycles are longer than a day, e.g. menstrual cycle. Recently, the role of these rhythms in fighting disease and responding to medication has come under study by researchers and scientists. The coordination of medical treatment and drug delivery with such biological clocks and rhythms is termed Chronotherapy.

In chronopharmacotherapy, drug administration is synchronized with circadian rhythms. If the peak of symptoms occur at daytime a conventional dosage forms can be administrated just before the symptoms are worsening. If symptoms of the disease became worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration. In this case, modified-release dosage forms must be used.

To introduce the concept of chronopharmaceutics, it is important to define the concepts of chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. Biological rhythms are defined by a

number of characteristics. The term "circadian" was coined by Franz Halberg from the Latin circa, meaning about, and dies, meaning day. Oscillations of shorter duration are termed ''ultradian'' (more than one cycle per 24 h). Oscillations that are longer than 24 h are ''infradian'' (less than one cycle per 24 h) rhythms. Ultradian, circadian, and infradian rhythms coexist at all levels of biologic organization.[3]

Chronobiological studies have established circadian rhythm for almost all body functions. They are in synchrony with sleep - activity cycle of the individual. The rhythms tend to fall into two groups. In the first are those that peak during the daytime and are associated with the activity phase of the individual: body temperature, mental, physical and gastrointestinal activities, blood pressure, heart rate, secretion of adrenaline etc. The second group, where rhythms show a peak during nocturnal sleep, includes secretion of several hormones, among which are growth hormone, cortisol and melatonin. Beside the physiological functions, the pathological states of disease have also circadian rhythms. Results of several epidemiological studies demonstrate the elevated risk of different pathology during 24-hour cycle.[1]

Pharmaceutics is an area of biomedical and pharmaceutical sciences that deals with the design and evaluation of pharmaceutical dosage forms (or drug delivery systems) to assure their safety, effectiveness, quality and reliability. Traditionally, drug delivery has meant getting a simple chemical absorbed predictably from the gut or from the site of injection. A second-generation drug delivery goal has been the perfection of continuous, constant rate (zero-order) delivery of bioactive agents. However, living organisms are not ''zero-order'' in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle in order to maximize desired and minimize undesired drug effects.

Based on the previous definitions **"chronopharmaceutics is a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy".** [2]

Ideally, chronopharmaceutical drug delivery systems (ChrDDS) should time-controlled and site-specific drug delivery systems. Advantages are safer, more effective and reliable therapeutic effect taking into account advances in chronobiology and chronopharmacology, system biology and nanomedicine. Evidence suggests that

an ideal ChrDDS should: (i) be non-toxic within approved limits of use, (ii) have a realtime and specific triggering biomarker for a given disease state, (iii) have a feed-back control system (e.g. self-regulated and adaptative capability to circadian rhythm and individual patient to differentiate between awake–sleep status), (iv) be biocompatible and biodegradable, especially for parenteral administration, (v) be easy to manufacture at economic cost, and (vi) be easy to administer in to patients in order to enhance compliance to dosage regimen. Such ideal ChrDDS is not yet available on the market. The majority of these features may be found at the interface of chronobiology, chronopharmacology, system biology and nanomedicine.

Figure1.1 Presents the overview of most serious diseases displaying significant daily variations. Many of circadian dependent diseases display acute symptoms in early morning hours or in the morning at awakening . Most asthma attacks occur at 04:00 to 06:00 hours. Nocturnal asthma is a complex interaction of several coincident circadian rhythms e.g. secretion of hydrocortisone and adrenalin. Ischaemic hearth diseases, such as angina pectoris, myocardial infraction and stroke manifests more frequently during the night or in the morning before breakfast. Rapid increase in blood pressure is mostly responsible for these attacks. In hypertensive and also in normotensive individuals the blood pressure arises notably before awakening. Symptoms of rheumatoid arthritis and osteoarthritis have significant circadian rhythm. Stiffness and pain are greatest on awakening or in the early morning. Circadian rhythm of level of interleukin-6 is in good correlation with the rhythm of symptoms of rheumatoid arthritis. Dyspnoea and peak of expiratory flow values have been found to become worse during the night.

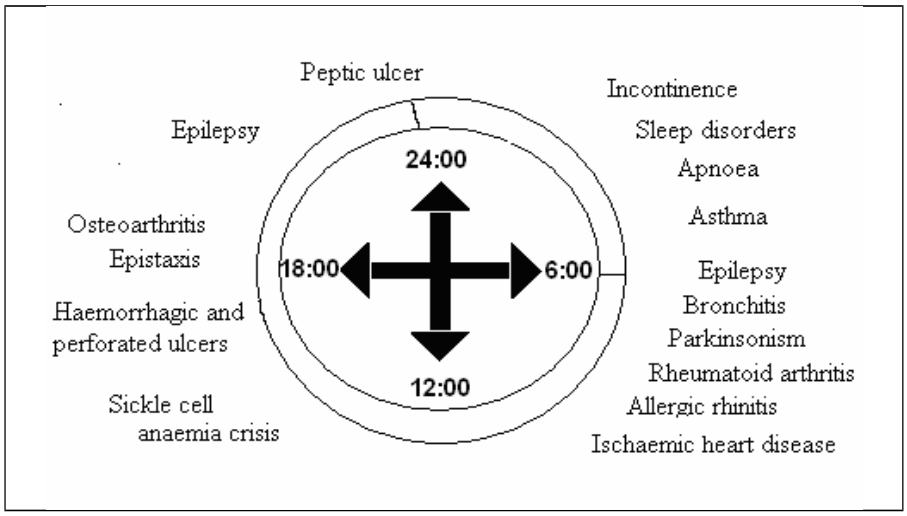

Fig.1.1: Disease Displaying Circadian Rhythm

1.2 TIME-CONTROLLED RELEASE DOSAGE FORMS [4-5]

Oral drug delivery is the most popular and convenient form of the drug administration. Evolution of oral solid dosage forms on the basis of dissolution profile:

• From 1950-s. conventional (immediate release) dosage forms

• From 1960-s. prolonged-release (sustained-release) dosage forms

• From late 1980-s. pulsatile or prolonged-release dosage forms following a lag period.

Modified-release formulations have many advantages over immediate-release formulations. With these formulations a less frequent drug administration is possible, lower peak concentrations can be obtained to avoid adverse effects and patient compliance can be improved. The modified-release dosage forms can be divided into subgroups of rate-controlled-release, delayed-release and pulsed-release formulations. Delayed-release formulations include time-controlled release and site-specific dosage forms. Time-delayed delivery system (time-controlled release formulations and pulsed release formulations) is the best approach to deliver drugs in accordance with circadian rhythms of the disease. The mentioned approach serves a purpose especially in the treatment of early morning symptoms. By timing the drug administration, plasma peak is obtained at an optimal time. Number of doses per day can be reduced. When there are no symptoms, there is no need for drugs. First pass metabolism and tolerance development can also be avoided.

The influence on chronokinetic of the route of administration must also be considered. For example, there are studies showing that chronopharmacokinetic variation is not found when drug is administrated rectally. Circadian variation in the activity of many gastrointestinal, hepatic and renal processes could explain why the absorption, distribution, metabolism and excretion of drugs change as a function of the time of administration. The drug absorption process can be altered by factors as the structure of membrane, the physicochemical properties of drugs, the pH, the rate of gastric emptying and the motility the blood flow to the gastrointestinal tract. No study is available presently on temporal variations in the structure of membranes or on the effect of circadian changes of pH on drug absorption.

1.3 CHRONOPHARMACEUTICAL DRUG DELIVERY SYSTEM [2]

Controlled drug delivery systems have acquired a center stage in the arena of pharmaceutical R&D business. Such systems offer temporal and/or spatial control over the release of drug and grant a new lease of life to a drug molecule in terms of patentability**.** These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance. The oral controlled-release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action. Thus, the release commences as soon as the dosage form is administered as in the case of conventional dosage forms**.**

There are certain conditions for which continuous conventional controlled release pattern is not suitable. These conditions demand release of drug after a lag time. Therefore require a pulsatile delivery. A pulsatile drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid drug release. The first pulsed delivery formulation that released the active substance at a precisely defined time point was developed in the early 1990s. In this context, the aim of the research was to achieve a so-called sigmoidal release pattern. The characteristic feature of the formulation was a defined lag time followed by a drug pulse with the enclosed active quantity being released at once.

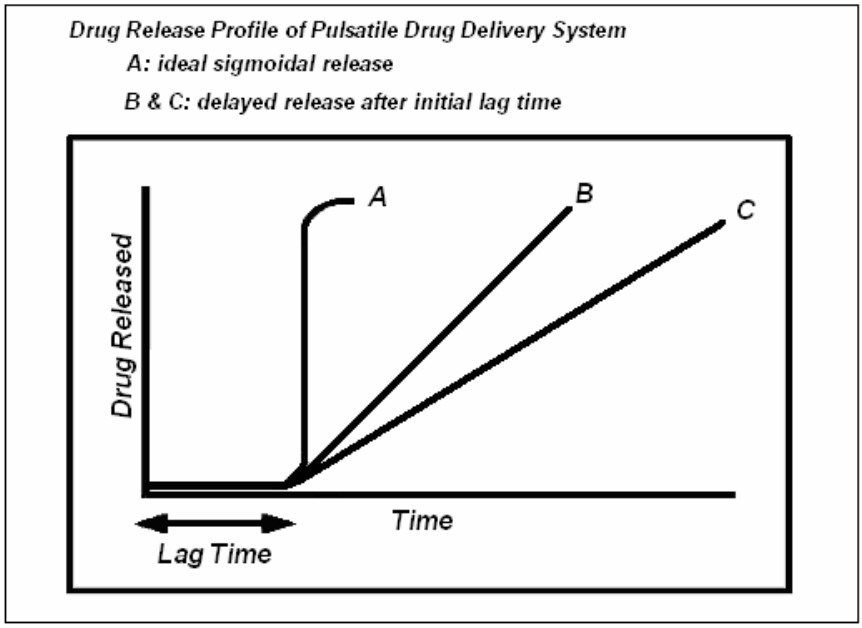

Fig.1.2: Drug Release Profile of Pulsatile Drug Delivery System

Thus, the major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time. Often, the drug is released over an extended period of time.

1.3.1 Currently reported systems [3-7]

Pulsatile systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastro-intestinal motility, etc. These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit (e.g., pellets) systems.

1.3.1.1 Single unit system

1.3.1.1.1. Capsular systems

Different single-unit capsular pulsatile drug delivery systems have been developed. A general architecture of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion or dissolution.

1.3.1.1.2. Pulsincap systems

The Pulsincap system is made up of a water-insoluble capsule body filled with drug formulation**.** The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a lag time. This is followed by a rapid drug release. Manipulating the dimension and the position of the plug can control the lag time.

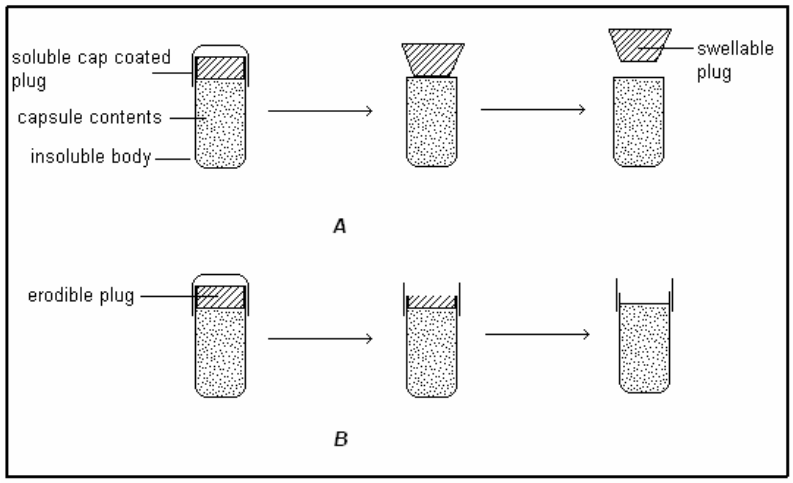

Fig. 1.3: Pulsatile release from an insoluble capsule body (Coated swellable plug; and Erodible plug Capsular System Based on Osmosis)

The plug material consists of insoluble but permeable and swellable polymers (eg, polymethacrylates), erodible compressed polymers (eg, hydroxypropylmethyl

cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (eg, saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (e.g. pectin). These formulations were well tolerated in animals and healthy volunteers, and there were no reports of gastro-intestinal irritation. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine.

1.3.1.1.3. Port systems

The Port System consists of a gelatin capsule coated with a semi permeable membrane (eg, cellulose acetate, PLGA) housing an insoluble plug (eg, lipidic) and an osmotically active agents ($NaHCo_3$, Citric acid) along with the drug formulation (Fig.1.5.).When in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. Coating thickness controls the lag time. The system was proposed to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in school-age children. Such a system avoids a second daily dose that otherwise would have been administered by a nurse during school hours.

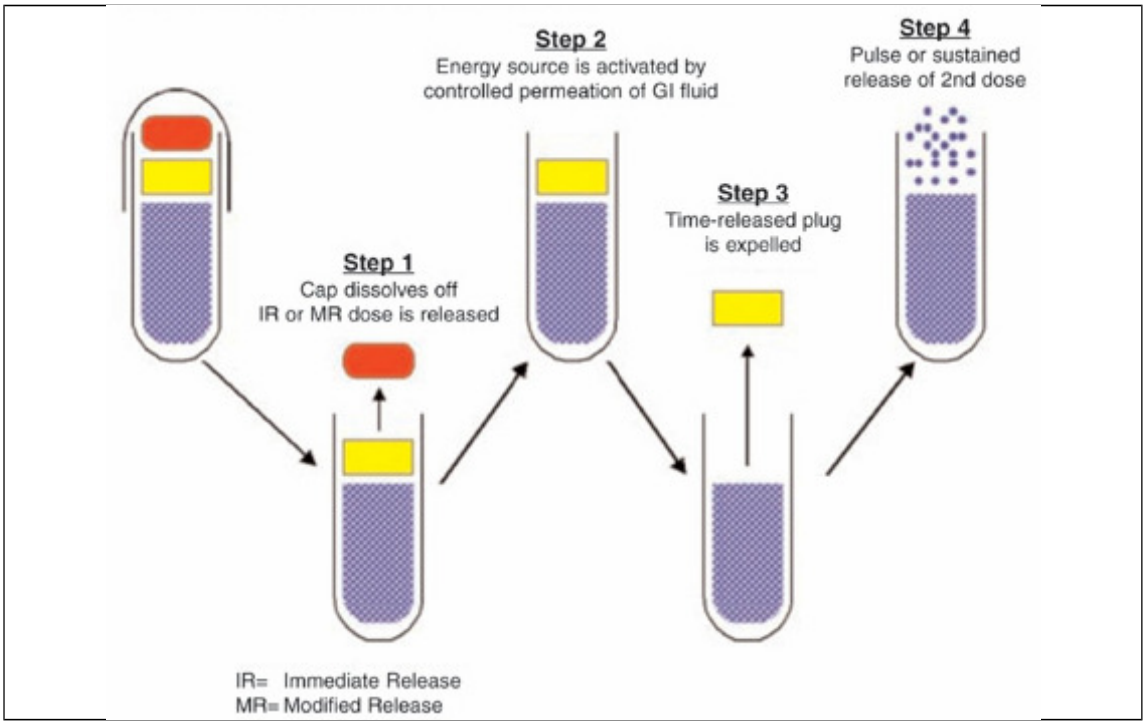

Fig.1.4: Drug Release Mechanism from PORT System.

1.3.1.1.4. A System based on expandable orifice [2-3]

To deliver the drug in liquid form, an osmotically driven capsular system was developed in which the liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved**.** The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body. The capsule wall is made up of an elastic material and possesses an orifice. As the osmosis proceeds, the pressure within the capsule rises, causing the wall to stretch. The orifice is small enough so that when the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall is distended beyond threshold value, the orifice expands sufficiently to allow drug release at a required rate. Elastomers, such as styrene-butadiene copolymer have been suggested. Pulsatile release was achieved after lag times of 1 to 10 hours, depending on the thickness of the barrier layer and that of semipermeable membrane, and a capsule designed for implantation can deliver drug intermittently at intervals of 6 hours for 2 days.

1.3.1.1.5. Delivery by a series of stops [2]

The implantable capsules containing a drug and a water-absorptive osmotic engine are placed in compartments separated by a movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level. The number of stops and the longitudinal placements of the stops along the length of the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity. This system was used to deliver porcine somatotropin**.**

1.3.1.1.6. Pulsatile delivery by solubility modulation

The system was especially developed for delivery of salbutamol sulphate**.** The compositions contain the drug (salbutamol sulphate) and a modulating agent (sodium chloride, NaCl). The modulating agent can be a solid organic acid, inorganic salt, or organic salt. In order to control zero-order release period and commencement of pulsed release, ratio of drug/modulator can be varied. After the period of zero-order release, the drug is delivered as one large pulse.

1.3.1.1.7. Pulsatile systems with erodible or soluble barrier coating. [8]

Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly. The lag time depends on the thickness of the coating layer.

1.3.1.1.8. Time clock systems [2]

The Time Clock system consists of a solid dosage form coated with lipidic barriers containing carnuba wax and bees' wax along with surfactants, such as polyoxyethylene sorbitan monooleate**.** This coat erodes or emulsifies in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion. Such systems are better suited for water-soluble drugs. The major advantage of this system is its ease of manufacturing without any need of special equipment. However, such lipid-based systems may have high in-vivo variability (eg, food effects).

1.3.1.1.9. Chronotropic systems [2]

The Chronotropic system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release**.** In addition, through the application of an outer gastric-resistant enteric film, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time**.** The lag time is controlled by the thickness and the viscosity grades of HPMC.

1.3.1.1.10. Multilayered tablet

A release pattern with two pulses was obtained from a three-layered tablet containing two drug containing layers separated by a drug-free gellable polymeric barrier layer. This three-layered tablet was coated on three sides with in impermeable ethyl cellulose, and the top portion was left uncoated. Upon contact with dissolution medium, the initial dose incorporated into the top layer was released rapidly from the non-coated surface. The second pulse was obtained from the bottom layer after the gelling barrier layer of HPMC was eroded and dissolved. The rate of gelling and/or dissolution of the barrier layer control the appearance of the second pulse. The gelling polymers reported include cellulose derivatives like HPMC, methyl cellulose, or polyvinyl alcohols of various molecular weights and the coating materials include ethyl cellulose, cellulose-acetate-propionate, methacrylic polymers, acrylic and mehtacrylic co-polymers, and polyalcohols**.**

1.3.1.1.11. Pulsatile systems with rupturable coating [8]

The effervescent excipients, swelling agents, or osmotic pressure can achieve the pressure necessary for the rupture of the coating. An effervescent mixture of citric acid and sodium bicarbonate was incorporated in a tablet core coated with ethyl cellulose. The carbon dioxide developed after penetration of water into the core resulted in a pulsatile release of drug after rupture of the coating. The release may depend on the mechanical properties of the coating layer**.** The highly swellable agents, also called superdisintegrants, are used to design a capsule-based system comprising a drug, swelling agent, and rupturable polymer layer**.** The lag time is function of the composition of the outer polymer layer. The presence of hydrophilic polymer like HPMC reduces the lag time. The system can be used for delivery of both solid and liquid drug formulations. A reservoir system with a semipermeable coating was designed for delivery of drugs that exhibit extensive first-pass metabolism. The release pattern was similar to that obtained after administration of several immediate-release doses**.**

1.3.1.2. Multiparticulate systems

Multiparticulate systems (e.g., pellets) offer various advantages over single unit systems. These include no risk of dose dumping, flexibility of blending units with different release patterns, and reproducible and short gastric residence time. But the drug-carrying capacity of multiparticulate systems is lower due to presence of higher quantity of excipients. Such systems are invariably a reservoir type with either rupturable or altered permeability coating**.**

1.3.1.2.1. Pulsatile system based on rupturable coating [8]

Time controlled explosion system: This is a multiparticulate system in which drug is coated on non pareil sugar seeds followed by a swellable layer and an insoluble top layer. The swelling agents used include superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, hydroxypropyl cellulose, polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc. Alternatively, an effervescent system comprising a mixture of tartaric acid and sodium bicarbonate may also be used. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The release is independent of environmental factors like pH and drug solubility. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer. A rapid release after the lag phase was achieved with increased

concentration of osmotic agent. Invivo studies of time-controlled explosion system (TCES) with an invitro lag time of three hours showed appearance of drug in blood after 3 hours, and maximum blood levels after 5 hours.

1.3.1.2.2. Osmotic based rupturable coating systems [3,9-10]

Permeability controlled system: This system is based on a combination of osmotic and swelling effects. The core containing the drug, a low bulk density solid and/or liquid lipid material (eg, mineral oil) and a disintegrant was prepared. This core was then coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coating.

The use of osmotically active agents that do not undergo swelling was reported by Schultz and Kleinebudde. The pellet cores consisted of drug and sodium chloride. These were coated with a semipermeable cellulose acetate polymer. This polymer is selectively permeable to water and is impermeable to the drug. The lag time increased with increase in the coating thickness and with higher amounts of talc or lipophilic plasticizer in the coating. The sodium chloride facilitated the desired fast release of drug. In absence of sodium chloride, a sustained release was obtained after the lag time due to a lower degree of core swelling that resulted in generation of small fissures.

Chen has also proposed a system containing a core of drug and osmotically active agent (sodium chloride) coated with an insoluble permeable membrane. The coating materials reported include different types of poly (acrylate-methacrylate) copolymers and magnesium stearate, which reduces water permeability of the membrane, thus allowing for use of thinner films. Thicker films are to be avoided as they do not rupture completely. Using ethyl cellulose as a coating material, it was possible to affect lag time of enteric polymer to achieve rupturing after a predetermined time.

1.3.1.2.3. Pulsatile delivery by change in membrane permeability [2-3]

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter ions in the medium**.** Several delivery systems based on this ion exchange have been developed. Eudragit RS 30D is reported to be a polymer of choice for this purpose. It typically contains positively polarized quaternary ammonium group in the polymer side chain,

which is always accompanied by negative hydrochloride counter ions. The ammonium group being hydrophilic facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time. The cores were prepared using theophylline as model drug and sodium acetate. These pellets were coated using Eudragit RS30D (10% to 40% weight gain) in four different layer thicknesses. A correlation between film thickness and lag time was observed. After the lag time, interaction between the acetate and polymer increases the permeability of the coating so significantly that the entire active dose is liberated within a few minutes. The lag time increases with increasing thickness of the coat, but the release of the drug was found to be independent of this thickness and depended on the amount of salt present in the system.

1.3.1.2.4. Sigmoidal release systems [4]

This consists of pellet cores comprising drug and succinic acid coated with ammonio methacrylate copolymer USP/NF type B. The lag time is controlled by the rate of water influx through the polymer membrane. The water mix with succinic acid, and the drug in the core and the acid solution in turn increases permeability of the hydrated polymer film. In addition to succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid can be used. The increased permeability can be explained by improved hydration of film, which increases free volume.[34, 35]

1.3.1.3. Other systems

1.3.1.3.1. Enzyme containing capsular shaped pulsatile drug delivery systems

Krogel I. et al (1999) developed and evaluated an alternative pulsatile drug delivery system consisting of a drug containing, impermeable capsule body closed with an enzyme degradable plug. The degradation of plug material was not controlled by enzymes being present in the GIT, but by an enzyme being directly incorporated in the plug. The enzyme degradable plug consisted of the natural polysaccharide pectin, which is widely used in the food industry as a thickening agent and a pectinolytic enzyme mix. In this system pulsatile drug release is enzymatically controlled which is based on an impermeable capsule body which contains the drug and is closed by an erodible pectin / pectinase plug.

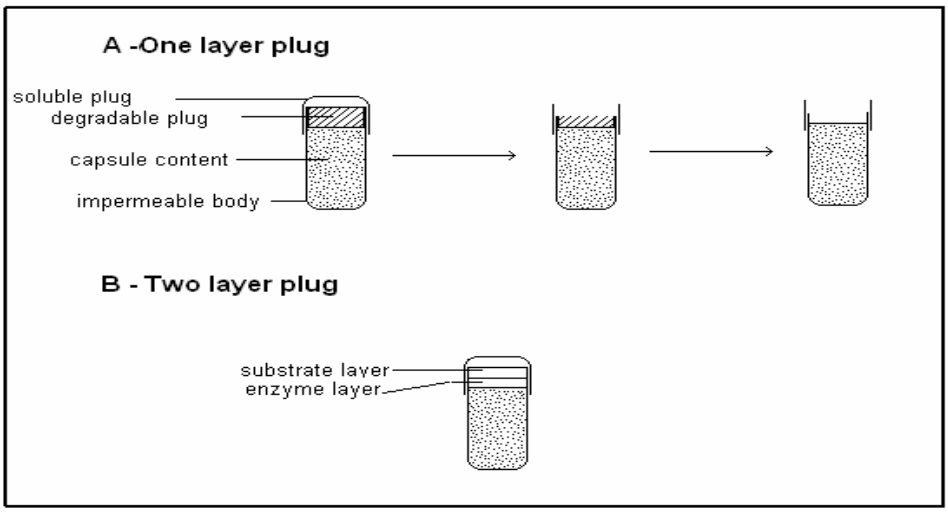

Fig.1.5: Schematic diagram of a one layer pulsatile DDS with an impermeable capsule body and pulsatile DDS with a two layer plug.

The powder (pectin and pectinolytic enzyme in different ratios) was blended and plug was prepared by direct compression with single punch press. The compressed plug was placed manually within the orifice of the drug filled poly (propylene) capsule body, with the top of the capsule body and the plug being even. The enzyme free layer of the two layers, plug was on the top of the capsule. The plug that consist of a mixture of enzyme degradable polymer and the enzyme, acts as release barrier. The polymer is degraded by enzyme after aqueous contact. Ideally no drug is released until the complete plug is degraded, leading to a defined lag time prior to the drug release. The two layer plug was prepared to separate the polymeric substance from the enzyme and to protect enzyme from the possibly degrading enzyme in GIT fluid. However, the lag time prior to drug release from the two layer DDS was longer then 6 hour and the subsequent drug release occurs in the sustained not in the pulsatile manner because the plug material was not completely emptied from the orifice. Hence one layered system is more important for study.

1.3.1.3.2. Modified pulsincap technique

Murthy et al (2001) developed modified pulsincap preparation for rifampicin release studies of various hydrophilic polymers, such as Guar gum, Carbopol 940, Sodium alginate, HPMC, Methyl cellulose, Gum karaya and poly vinyl alcohol. Increase in the hydrophilic polymer content results in reduction in the release rate of the drug. Pulsincap was a patented preparation, consisting of hardened capsule body filled with basic drug mixture and sealed with hydrogel plug. After embedding sufficient amount of water the hydrogel plug will be released at predetermined time

and the total content of the capsule will be released into the GIT fluids. Hence this preparation is regarded as time release dosages form. In modified pulsincap, the drug polymer mixture is filled into the capsule body. The release rate of the drug was controlled by the formation of the viscous hydrogel within the capsule body. This technique controls the drug release rate whereas pulsincap preparation controls the drug release time.

1.3.1.3.3. Configuration of tablet matrix in impermeable cylinder

A multifunctional drug delivery system based on HPMC matrices placed within an impermeable polymeric cylinder (open at both ends) was developed. Depending on the configuration of the device, extended release, floating or pulsatile drug delivery system could be obtained. This system can be of three types:

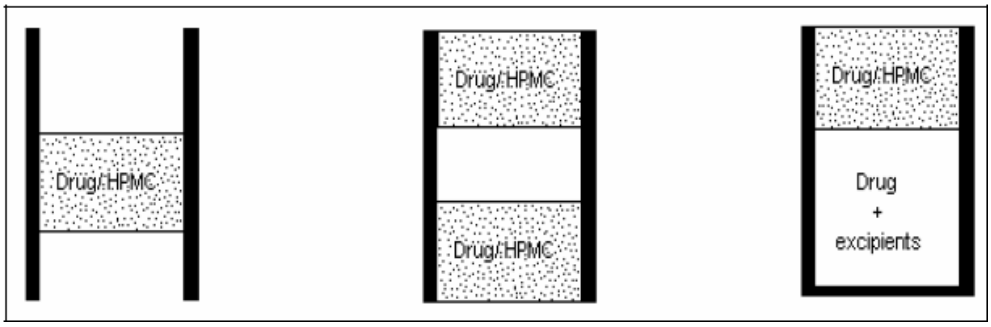

Fig.1.6: Configuration of multifunctional matrix delivery system.

1. One drug containing tablet within an impermeable cylinder.
2. Floating device (one tablet at each end of the cylinder with an air filled space in the middle).
3. Pulsatile system (drug filled impermeable capsule half closed with an erodible drug free plug).

The release behavior of the different devices was investigated as a function of HPMC viscosity grade, HPMC content, type of drug, matrix weight, and position of the matrix within the polymer cylinder, addition of various fillers and agitation rate of the release medium. Drug release increases with reduce HPMC viscosity grade, higher aqueous drug solubility, decrease HPMC content and increase surface area of the matrix. The release was fairly independent on the agitation rate, the position of the tablet within the polymeric cylinder and length of the cylinder. With the pulsatile device, the lag time prior to drug release could be controlled through the erosion rate of the matrix.

1.3.1.3.4. Stimuli induced pulsatile release [4-5]

1.3.1.3.4.1. Thermo responsive hydrogel systems

In closed loop systems, or self regulated systems, the release is in direct response to the conditions detected the temperature, type of solvent, pH, or concentration. Poly (N-isopropylacrylamide) (PIPAAM) is a well known example of a thermo responsive polymer. At its transition of 32ºC, the polymer is soluble in water; but, as temperature is increased, the polymer precipitates and phase separates. Poly (ethylene glycol) and poly (propylene glycol) copolymers and poly (lactic acid) and poly (glycolic acid) copolymers also exhibit thermo responsiveness. These polymers are useful in developing thermo gelling systems (Atridox); the drug is dissolved in the liquid form of the polymer at room temperature. When this mixture is injected in the body, the polymer turns into a gel, which eventually degrades and releases the drug molecules. Drug release from the PIPAAM hydrogel at temperature below 32◦C was governed by diffusion, while above this drug release was stopped completely due to skin layer formation on the gel surface. Akihiko Kikuchi et al (2004) have recently reported a new method to accelerate gel swelling / deswelling kinetics based on molecular design of the gel structure. Free mobile linear PIPAAM chains were grafted within the crossed linked PIPAAM hydrogels. The drug release profile from the graft type PIPAAM gels were monitored after the immersion of the drug containing gels in a suitable release medium. Low molecular weight sodium salicylate was released in one burst from conventional PIPAAM gels immediately after a temperature increased, after which the release terminated due to formation of a dense impermeable skin layer on the surface.

1.3.1.3.4.2. Thermoresponsive polymeric micelle systems

Kataoka et al (2001) comprehensively reviewed the properties and biological response of polymeric micelles making them the most noteworthy candidate as drug carrier for the treatment of cancer. The polymeric micelle is composed of amphiphilic block copolymers exhibiting a hydrophobic core with a hydrophilic corona. Due to this unique structure characteristic, polymer micelle exhibits characteristics that are not detected by the reticuloendothelial system (RES). Thus the passive targeting could be achieved through a enhanced permeation retention effect of the tumor sites. Blockco polymers formed micellar structure (with core shell structure) in aqueous

solution below Tg temperature. The micelle formation was confirmed by dynamic light scattering measurements.

1.3.1.3.5. Chemical stimuli induced pulsatile release

1.3.1.3.5.1. Glucose responsive insulin release devices

Self regulating insulin delivery devices depend on the concentration of glucose in the blood to control the release of insulin. Ishihara et al (1983) prepared one gel membrane system to regulate the insulin permeability. The system proposed immobilizing glucose oxidase (an enzyme) to a pH responsive polymeric hydrogel, which encloses a saturated insulin solution. At high glucose levels, glucose is catalyzed by glucose oxidase and converts it to gluconic acid, thus lowering the pH. This decrease in pH causes the membrane to swell, forcing the insulin out of the device.

1.3.1.3.5.2. Inflammation induced pulsatile release

During inflammation, hydroxyl radicals (-OH) are produced from the inflammation responsive cells. Yui et al (1993) focused on the inflammatory induced hydroxyl radicals and designed drug delivery system, which responded to hydroxyl radicals and degraded in a limited manner. In the body hyaluronic acid (HA) is degraded either by specific enzyme, hyaluronidase, or hydroxyl radicals. Thus they prepared crossed linked HA with ethylene glycol di-glyceride ether. When microspheres were incorporated in the HA hydrogel as a model drug, these microspheres were released only when hydroxyl radicals induced HA gel degradation. Control HA gel implanted in the animals were relatively stable over a period of 100 days. Thus it is possible to treat patients with inflammatory disease, such as rheumatoid arthritis, using anti-inflammatory drug incorporated HA gels as a new implantable drug delivery system.

1.3.1.3.5.3. Drug release from intelligent gels responding to antibody concentrations

There are numerous types of bioactive compounds, which exist in the body. Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/ deswelling characteristics. Miyata et al (1999) focused on the introduction of stimuli responsive cross-linking structure into hydrogels. A special attention was given to antigen antibody complex formation as the cross linking unit in the gel, because specific antigen recognition of an antibody can provide the basis for a new device fabrication. Utilizing the difference in

association constants between polymerized antibodies and naturally derived antibodies toward specific antigens, reversible gels swelling/ deswelling and drug permeation changes occurred. Thus the biological stimuli responsive hydrogels were created.

1.4 FLOATING PULSATILE DRUG DELIVERY SYSTEM [11]

There are numerous approaches to prolong gastric retention, floating drug delivery system is the most widely used technique and offers a simple practical approach to increased gastric residency through inherent buoyancy. Floating has been achieved with the preparation of low density dry solid systems (e.g. inclusion of sponges, highly porous systems) or with systems, which decrease in density upon contact with gastric fluids based on the expansion of swelling agents or CO_2 generation. Pulsatile drug delivery systems are characterized by two release phases, a first phase with no or little drug being released, followed by a second phase, during which the drug is released completely within a short period of time after the lag time. The release can be either time or site controlled. The release from the first group is essentially determined by the system, while the release from the second group is primarily controlled by the biological environment in the gastrointestinal tract Most pulsatile delivery systems are reservoir devices covered with a barrier coating, which dissolves erodes or ruptures after a certain time period, followed by rapid drug release from the reservoir. Reservoir type delivery systems based on the expansion of the core have been evaluated for both floating delivery systems having a lower density than gastrointestinal fluids, and for pulsatile systems in which the core expansion causes rupturing of the coating to allow rapid drug release.

The system consists of three different parts, a core tablet, containing the active ingredient, an erodible outer shell, and a top cover buoyant layer (Fig. 6.2). One layer is for buoyancy and the other for drug pulsatile release. The pulsatile release system with various lag times was prepared by compression with different erodible polymeric layers (press-coated systems) as described previously. Ideally, the novel system could result in (1) a floating dosage form with a prolonged gastric residence time and in (2) a pulsatile dosage form, in which the drug is released rapidly in a time controlled fashion after rupturing of the coating.

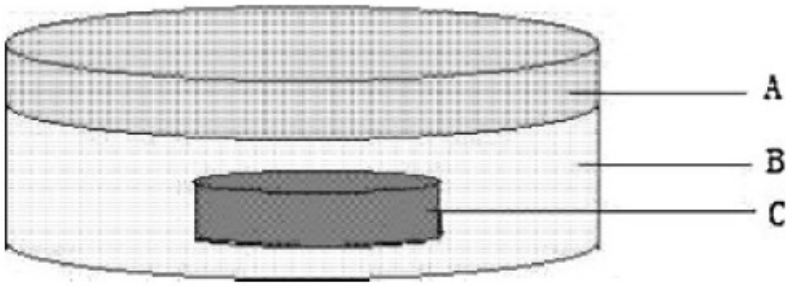

Figure 1.7. Schematic diagram of the floating–pulsatile release (FPRT) delivery system.

A: the layer for buoyancy; B: the layer for drug pulsatile release; C: the rapid-release core tablet.

1.5 PRESS COATING TECHNIQUE (COMPRESSION COATED TECHNIQUE) [2,12]

The addition of an IR component allows one to design delivery systems having optimal pharmacokinetic profiles and enables the combination of different drugs thereby improving patient compliance. To achieve this combination IR plus osmotic CR dosage form, bilayer systems may be prepared by spray coating a coated core CR tablet with a solution containing the IR drug either as part of the drug delivery rate controlling coating or on the outside of that coating. In spray coating the drug, it must either be dissolved or dispersed in the coating fluid. In many cases, dissolution of the drug results in stability issues, either because the drug itself is unstable in solution, or because in the spraying and drying process, the drug precipitates from solution in a less stable morphology (such as amorphous). For low solubility drugs, dissolution in an appropriate solvent may require high dilution with resulting prohibitively long coating run times. Although drug dispersions can be prepared and coated, many drugs present difficult challenges For example, the drug must be insoluble in the coating solvent. The drug must also be kept in suspension during the spray coating process. Content uniformity (tablet to tablet) tablet can be especially challenging if there is settling or agglomeration. The press coating technique offers advantages over liquid coating as it does not involve the use of solvents, requires a relatively short manufacturing process, and allows greater weight gain to the core tablet. However, common drawbacks of the press coating technique are the multi-step processes involved, and the requirement for reliable and reproducible central positioning of the core tablet within press coated tablet (PCT).

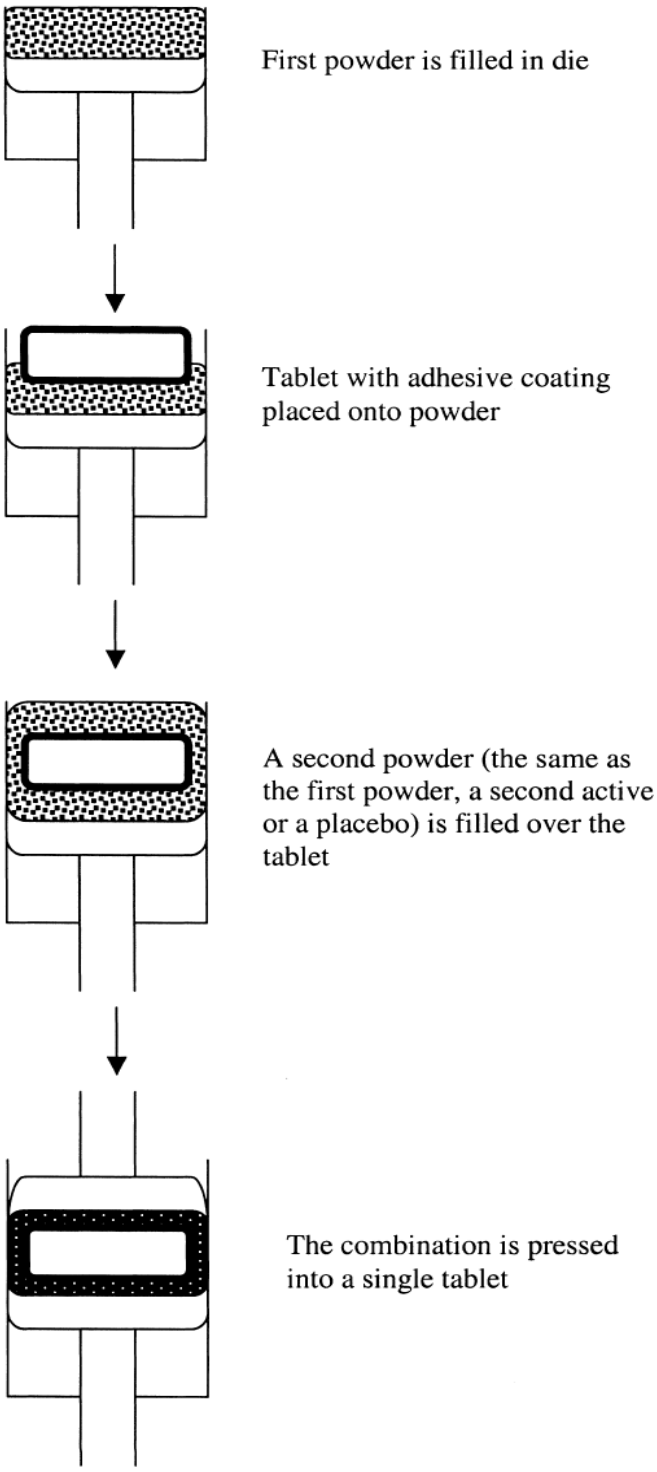

Fig.1.8: Press coating technique

1. Nifedipine is widely used for its anti-hypertension and anti-anginal properties. So nifedipine is a typical example of drug, which is used in the therapy of symptoms or diseases as described[28-29].

2. However, for such cases, conventional drug delivery systems are inappropriate for the delivery of Nifedipine, as they cannot be administered just before the symptoms anti-hypertension and anti-angina,because during this time the patients are asleep.[1-2]

3.Dossage form and dose [27-29]

Dossage form: Immediate release tablet and sustained release tablet

Dose: 20 mg

4. Advantages of pulsatie drug delievery systems are as follow [2]

a) Extended daytime or nighttime activity
b) Reduced side effects
c) Reduced dosage frequency
d) Reduction in dose size
e) Improved patient compliance
f) Drug adapts to suit circadian rhythms of body functions or diseases.
g) Drug targeting to specific site like colon.
h) Protection of mucosa from irritating drugs.
i) Drug loss is prevented by extensive first pass metabolism.

2. LITERATURE REVIEW

Huda et al. (2012) [13] formulated sustained release matrix tablets of a poorly water soluble drug nifedipine using hydrophilic polymers Methocel K15M CR and Methocel K100LV CR by direct compression method. The tablets were subjected to various tests for their physical parameters such as thickness, hardness and friability and in vitro release study was carried out for 12 hours using USP paddle type dissolution apparatus in phosphate buffer with sodium lauryl sulphate (pH 6.8). Quantitative evaluation by mathematical model indicates that formulation containing HPMC K15M CR and HPMC K100LV CR in a ratio of 1:3 showed better dissolution properties compared to other ratio. The study indicates that the hydrophilic matrix tablets of nifedipine prepared using Methocel K15M CR and Methocel K100LV CR can successfully be employed as twice a day oral controlled release dosage form in order to improve patient compliance.

Ghosh S et al (2010) [14] developed a sustained release matrix tablet formulation of water soluble Nifedipine hydrochloride using multi unit chitosan treated alginate. The addition of chitosan increased the swelling of multiple unit systems (MUS) in acidic conditions and reduced the drug release from MUS. The sustained release formulation of nifedipine is absorbed uniformly from the entire gastro intestinal tract. It is administrated orally in relatively small dose of 20 mg. This study shows that the matrix type chitosan treated alginate MUS can be used to formulate sustained release tablets to deliver nifedipine hydrochloride for more than 12 hours

Gosai A et al. (2008)[15] formulated orodispersible tablets of ondansetron hydrochloride. Because of its application in emesis condition, fast onset of action is desirable. Tablets were prepared by direct compression using sodium starch glycolate and croscarmellose as superdisintegrants, as the combination of these two superdisintegrants gives better disintegration of the tablet. The tablets were evaluated for weight variation, mechanical strength, in vitro disintegration time, in vivo disintegration time, wetting time, and drug release characteristics. Hardness and friability data indicated mechanical strength of tablets. The results of in vitro disintegration time and in vivo disintegration time indicated that the tablets dispersed rapidly in mouth within 3 to 5 seconds. Dissolution study revealed faster release rate

of ondansetron hydrochloride as compared marketed conventional tablet formulation of ondansetron hydrochloride. It was concluded that superdisintegrants addition technique is a useful method for preparing orodispersible tablets by direct compression method.

Rajendran N et al. (2011)[16] formulated immediate release tablets of olopatadine hydrochloride to study the effect of superdisintegrants and processing methods on the physicochemical and in-vitro release characteristics. Various formulations of olopatadine were prepared by direct compression, wet granulation and fluidized bed granulation methods to achieve maximum drug content with reference to innovator. Varying proportion of superdisintegrants such as crosspovidone XL, sodium starch glycolate, croscarmellose sodium used to compare drug release profile with innovator. Formulations were prepared and evaluated with respect to various precompression and postcompression parameters. The results indicate that the superdisintegrants used such as crosspovidone XL, sodium starch glycolate, croscarmellose sodium have influence on the disintegration time.

Deshmukh G et al (2011) [17] developed fast disintegrating tablets of Lamotrigine using Micro crystalline cellulose and Lactose Monohydrate IP as diluents and Aspartame as sweetening agent along with three different levels of two super disintegrants sodium starch glycolate and kyron T-314. Tablets were evaluated for weight variation, hardness, friability, thickness, wetting time, and disintegration time (DT) and dissolution study. The results of above experiments revealed that the concentration of super disintegrating agents, sodium starch glycolate and Kyron T 314 significantly affect the disintegration time of prepared tablets.

Metker V et al (2011)[18] developed mouth dissolving tablets of lornoxicam by wet granulation technique using kyron T-314 as superdisintegrant and menthol as subliming agent. Polacrillin Potassium (kyron T-314) is a cation exchange resin used in oral pharmaceutical formulation. From the study, it can be concluded that formulations prepared by sublimation technique gives better release profile and increase absorption of the drug. Formulations with kyron T-314 as superdisintegrant

disintegrates within few seconds without need of water and enhance absorption leading to its increased bioavailability.

Bhat A et al. (2011) [19] developed and evaluated a pulsatile drug delivery system based on impermeable capsule body filled with theophylline pellets and sealed with erodible polymer plug placed in the opening of capsule body. Erodible plugs were prepared by direct compression. Theophylline pellets were placed in the capsule by congealing a meltable plug material within the capsule opening. The theophylline pellets were prepared in four batches with PVP K30, water as binder solution and evaluated for the surface morphology, particle size, drug content and invitro release profile and from the obtained results; one best formulation was selected for further fabrication of pulsatile capsule. Different hydrogel polymers were used as plugs, to maintain a suitable lag period and it was found that the drug release was controlled by the proportion of polymers used. The lag time prior to pulsatile drug release correlated well with erosion properties of the plugs. Pulsatile drug release could be controlled by the composition of the plug and thickness of the plug. Programmable pulsatile release has been achieved from a capsule device over the period of 2–36 hours which is the requirement of chronopharmaceutical drug delivery.

Shah V et al. (2010) [20] developed formula for multiple unit system for pulsatile drug delivery of Salbutamol Sulphate which offered a solution for chronopharmacological behavior of asthma, extensive first-pass metabolism and necessity of night-time dosing. Among five Batches Specific batch with 4% of cellulose acetate phthalate (CAP) and 2% of ethyl cellulose (EC) gave late release than predetermined time. It released its higher dose after 6 hours. So that batch SF2 is accurate batch for nocturnal asthma according to pulsatile drug delivery system.

Okuda T et al. (2010) [21] developed formulation of biodegradable nanofiber meshes. Which enabled the time-programmed dual release in a single formulation. Multilayered drug-loaded biodegradable nanofiber meshes were designed using sequential electrospinning. First drug-loaded mesh (top), (ii) barrier mesh, (iii) second drug-loaded mesh, and (iv) basement mesh (bottom). The drug release speed and

duration were controlled by features of the electrospun meshes such as the fiber diameter and mesh thickness. Control of the timed release and retardation period of the second drug was accomplished by appropriate design of the barrier mesh thickness. An invitro release experiment demonstrated that the tetra-layered construction described above with appropriate morphological features of each component mesh can provide timed dual release of the respective drugs. The time programmed dual release system using the multilayered electrospun nanofiber meshes proved to be useful formulation for multidrug combination therapy which require regiospecific administration of two drugs at different times. These multilayered formulations can be used for biochemical modulation. That gives one administrative strategy for use of sequential chemotherapy employing multiple anti-tumor drugs.

Iskandar S. Moussa, Louis H. Cartilier (1997) [22]developed cross-linked amylose (CLA) press coated sustained drug delivery design dry coated tablets for time independent and complex drug release. To make the cores, CLA was mixed with the model drug in different proportions and then compressed. The cores were coated manually, consisting of either pure CLA or a mixture of CLA with a small proportion of solute. Diltiazem HC1 and acetaminophen were the model drugs used. CLA dry coated tablets behave as reservoir systems where the outer gel layer acts as a solution diffusion membrane, through which transport occurs by a process of dissolution of the permeating drug in the polymer at one interface and diffusion down a gradient in thermodynamic activity. After the drug has established a uniform concentration gradient within the outer membrane (lag time), drug release is linear for the range of constant thermodynamic activity in the core. For the same core composition, decreasing the coating thickness or incorporating small amounts of NaC1 in the shell shorten the release lag time and increase the release rate. By varying the drug to CLA ratio in the core we are able to optimize the release profiles. Zero order release profiles with or without a time delay were developed.

Efentakis M. et al (2006) [23] developed a dry coated drug deliverdy system with an impermeable cup, swellable top layer and pulsatile release. The system consists of three different parts, a core tablet, containing the active ingredient, an impermeable

outer shell and a top cover layer barrier of a soluble polymer. The core contained either diclofenac sodium or ketoprofen as model drugs. The impermeable coating cup consisted of cellulose acetate propionate and the top cover layer of hydrophilic swellable materials, such as polyethylene oxide, sodium alginate or sodium carboxymethyl cellulose. The effect of the core, the polymer characteristics and quantity at the top cover layer, on the lag time and drug release was investigated. The results showed the release of the drug after a certain lag time generally due to the erosion of the top cover layer. The quantity of the material, its characteristics (viscosity, swelling, gel layer thickness) and the drug solubility was found to modify lag time and drug release. The lag time increased when the quantity of top layer increased, whereas drug release decreased. The use of sodium carboxymethyl cellulose resulted in the greatest swelling, gel thickness and lag time, but the lowest drug release from the system. Polyethylene oxide showed an intermediate behaviour while, the sodium alginate exhibited the smallest swelling, gel thickness and the shortest lag time, but the fastest release. These findings suggest that drug delivery can be controlled by manipulation of these formulations.

Yan Zhang (2003) [24] Prepare a novel pulsed release system based on bilayer coated tablets containing an osmotically active agent. Hydroxy propyl methyl cellulose (HPMC) and the mixture of Eudragit RS and RL were applied as the swelling layer and semi permeable outer coat, respectively. To examine the mechanism of drug release from this pulsed release system, drug release behaviors were investigated under conditions of various osmotic pressures. Both lag time and release rate were dependent on the coating level and the osmotic pressure of the dissolution medium. The swelling of tablets and the dynamics of water uptake during the dissolution were investigated to further elucidate the mechanism of drug release. The osmotic active agent induces a continuous water influx resulting in a rapid expansion of the membrane. The subsequent formation of fractures leads to a fast drug release after an initial lag time. All the results obtained in the present study indicated that both diffusion and osmotic pumping effect were involved in drug release from the device, but the latter was more dominant.

Janugade B. et al (2009) [25] formulated an oral press coated tablet by using direct compression and wet granulation method to achieve the predetermined lag time. This press coated tablets containing montelukast sodium in the inner core was formulated with an outer barrier layer by different compositions of hydrophobic polymer ethyl cellulose and hydrophilic polymer low substituted hydroxyl propyl cellulose. The effect of formulation composition on the barrier layer comprising both hydrophobic and hydrophilic excipients on the lag time of drug release was investigated. It was observed that lag time decreases with increasing concentration of low substituted hydroxyl propyl cellulose. Press coated tablets coated by dry mixing and by wet granulation showed variations in lag time. As compared to dry mixed blend method wet granulation method gives less lag time.

Kimberly D. et al. (2009) [26] evaluated pulsatile dosing of clarithromycin and amoxicillin alone or combined against Streptococcus pneumoniae with various susceptibilities. Pulsatile amoxicillin when combined with clarithromycin was proved to be superior to 8 or 12 h dosing intermediate strain and was identical for the susceptible strain.

Salunkhe A et al (2011) [11] prepared and evaluated a floating pulsatile drug delivery system of metoprolol tartrate. The prepared floating pulsatile delivery system consisted of three different parts a core tablet containing the active ingredient, an erodible outer shell and a top cover buoyant layer. The rapid release core tablet (RRCT) was prepared by using superdisintegrants along with active ingredients. Dry coating of optimized RRCT was done by using different grades of hydroxy propyl methyl cellulose (HPMC) E5, E15, and E50 and upper most buoyant layer was prepared with HPMC K15M and sodium bicarbonate. Formulations were evaluated for their physical characteristics, drug content, invitro disintegration time, drug release profile, floating lag time, floating time and invivo X ray study. On the basis of these evaluation parameters it was found that optimized floating pulsatile release formulation (FPRT) F9 showed floating lag time of 4 min, floating time of 12 hrs and release lag time of 6 hrs. The F9 formulation showed compliance with chronotherapeutic objective of hypertension.

Jagdale S et al (2010) [12] developed novel colon targeted tablet formulation by press coating rapidly disintegrating tablet of Atenolol with guar gum and Eudragit L100 as barrier layer. The entire device was enteric coated so that variability in gastric emptying time can be overcome and a colon specific release can be achieved. Different ratios of polymers were selected to achieve suitable lag time for the treatment of angina pectoris. Invitro release studies for prepared tablets were carried out for 2 h in 0.1 N HCl, 3 h in pH 7.4 phosphate buffer and 6 h in simulated colonic fluid. In vitro studies revealed that the tablet coated with guar gum and Eudragit L100 have limited drug release in stomach and small intestinal environment and released maximum amount of drug in the colonic environment.

3 AIM AND OBJECTIVE

Aim

To develop and evaluate floating-pulsatile System for a cardiovascular drug, Nifedipine; with a four-five hour delay in release after oral administration. So that the dose administered at bedtime, drug is released after the initial delay such that maximum plasma level occurs in the early morning hours, when the patient is most at risk.

Objective

1) Preformulation studies
2) Selection of the appropriate excipients
3) Formulation of pulsatile floating tablet
4) To evaluate and characterize the prepared formulations
5) Stability studies of prepared optimized formulation
6) To study pharmacokinetics of pulsatile floating tablet

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4 PLANE OF WORK

1. Literature Survey.
2. Formulation of tablet
    - Selection of superdisintegrant & excipients which is used in core tablet.
    - Preparation of core tablet.
    - Preliminary batches of combined buoyant polymers for pulsatile release tablets.
    - Preparation of buoyant layer.
    - Preparation of pulsatile release tablet.
3. Evaluation of all pulsatile release tablet:
    - Physical parameters (Friability test, Hardness test, Drug content study, Loss on drying)
    - Assay
    - Dissolution testing
4. Selection of the optimized tablets.
5. To perform stability testing of the optimized formulations.
6. Pharmacokinetic study

5. MATERIAL AND INSTRUMENTS

Table 5.1 Instruments list

Instrument	**Make**	**Model no.**
Analytical Balance	Shimadzu	AUW220D
Balance	NHBAAE	LC-T
Sieves	Retch	--
Tablet compression machine	Cadmach, Ahmedabad	
Dissolution test apparatus	Electro Lab	TDT-08L
UV Spectrophotometer	UB Varian Cary 100 scan	EL 08053091
FTIR Spectrophotometer	Varian	640-IR
pH meter	Equip – tronics	EQ 621
Stability Chamber	Thermolab	--

Table 5.2: List of the material

Ingredients	**Grade**	**Category**	**Manufacturer**
Nifedipine	BP	Active	Polydrug
Crosscarmellose sodium	USP	Superdisintegrant	Western pharma
KYRON T314	BP	Superdisintegrant	Corel pharma.
Magnesium Stearate	BP	Lubricant	Western pharma
Lactose	BP	Diluent	Western pharma
HPMC K4M	BP	Polymer	S D Fine Chemicals
Carboxymethyl cellulose sodium(NaCMC)	BP	Polymer	S D Fine Chemicals
HPMC E15LV	BP	Polymer	S D Fine Chemicals
HPMC K100M	BP	Polymer	S D Fine Chemicals
Sodium bicarbonate	BP	Effervescent agent	S D Fine Chemicals
Citric acid	BP	Buffering agent	S D Fine Chemicals

5.1. DRUG PROFILE [27-29]

NIFEDIPINE

5.1. 1. Chemical Name **:** Dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

5.1.2. Chemical Formula **:** $C_{17}H_{18}N_2O_6$

5.1.3. Molecular Weight **:** 346.3 g/mol

5.1.4. Official status **:** BP

5.1.5. Organoleptic Properties : Yellow, crystalline powder.

5.1.6. Chemical Structure :

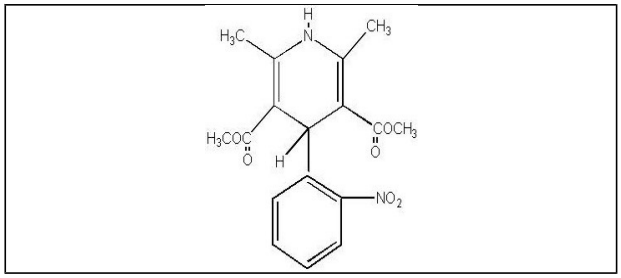


Fig 5.1: Chemical Structure Of Nifedipine

5.1.7. Physical properties

Table 5.3: Physical properties of Nifedipine BP

Nature and Description	Yellow, crystalline powder.
Solubility	Practically insoluble in water, freely soluble in acetone, sparingly soluble in ethanol.
Melting Point	171 °C-175°C.
Log p	1.82-2.49
Hygroscopicity	Non-hygroscopic

5.1.8. Chemical properties

Table No.5.4: Chemical properties of Nifedipine BP

pH	6.8-7.4
Photosensitivity	Photosensitive
Purity/Assay	98.0% - 102.0%
UV absorption	236 nm

Table No.5.5: Clinical pharmacological properties of Nifedipine BP

Therapeutic Class	Antihypertensive
Mechanism of Action	Nifedipine, prototype of the dihydropyridines, inhibits the influx of calcium ions into cardiac and vascular muscle cells like diltiazem and verapamil. On the contrary to these two drugs, nifedipine reduces the peripheral arterial vascular resistance and releases coronary artery spasms. Nifedipine thus has hypotensive and antianginal properties.
Route of Administration	Oral/ intravenous
Bioavailability	12%
Drug-Drug Interactions	Cimetidine can cause a reinforced effect of nifedipine through enzyme inhibition. Nifedipine can raise phenytoin and theophylline plasma levels. Unfavourable interactions with betablockers and digoxin have been suspected but were not confirmed clinically
BCS Classification	Class II
Adverse Effects	Nifedipine causes symptomatic side-effects in 20 to 30% of the treated subjects. These are based primarily on its vasodilating properties and can be reduced through combinations with beta-blockers. 5 to 12% complain about headaches, hot flushes, paresthesias, palpitations, vertigo, legedemas and gastrointestinal problems. Fatigue, impaired reaction and orthostatic hypotension are not as common. Significant deterioration has been observed repeatedly when nifedipine was used for left ventricular failure. Occasionally nifedipine causes an increase of myocardial ischemias.

5.1.10 Pharmacokinetic/ Pharmacodynamic data:

Table No.5.6: Pharmacokinetic/ Pharmacodynamic data Nifedipine BP

T ½ (hr)	2-3
Bioavailability	Great variability In Average 50%
Metabolism	Hepatic
Route of Excretion	Renal

5.1.11. Over dosage

Several cases of overdosage have been reported, some leading to death. Potential signs and symptoms associated with overdosage with Nifedipine are bradycardia, hypotension, bronchospasm, and cardiac failure.

5.1.12. Absorption and distribution

In man, absorption of Nifedipine is rapid and complete. Plasma levels following oral administration of conventional Nifedipine tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism. Nifedipine crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration.

5.1.13. Metabolism

Nifedipine is metabolized predominantly by CYP2D5, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D5 can be inhibited by a number of drugs. Concomitant use of inhibiting drugs in poor metabolizers will increase blood levels of Nifedipine several-fold, decreasing Nifedipine's cardioselectivity.

5.1.14. Elimination

Elimination is mainly by biotransformation in the liver, and the plasma half life ranges from approximately 2 to 3 hours. Less than 1% of an oral dose of Nifedipine is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no calcium channel-blocking activity. Following intravenous administration of Nifedipine, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of Nifedipine in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

5.2. EXCIPIENT PROFILE

5.2.1. Hypromellose [30-31]

Synonyms	Hydroxypropyl methylcellulose; hypromellosum; Methocel;
Chemical Name	Cellulose hydroxypropyl methyl ether
Molecular Weight	10 000–1 500 000.
Functional Category	Bioadhesive material; coating agent; controlled-release agent;dispersing agent; dissolution enhancer; emulsifying agent; emulsionstabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent
Solubility	Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol.
Loss on Drying	Not more than 5%
Density	0.341 g/cm^3
Viscosity	Methocel K4M: 4000 mPas Methocel K100M: 100 000 mPas Methocel E15 LV: 15 mPas
Stability and Storage Conditions	Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.
Incompatibilities	Hypromellose is incompatible with some oxidizing agents
Applications	Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations.

5.2.2. Carboxymethylcellulose sodium [32-33]

Synonyms	Akucell; Aqualon CMC; Aquasorb; Blanose; Carbose D; carmellosum natricum; Cel-O Brandt; cellulose gum; Cethylose
Chemical Name	Cellulose, carboxymethyl ether, sodium salt
Functional Category	Emulsifying agent; coating agent; stabilizing agent; suspending agent; tablet and capsule disintegrant; viscosity-increasing agent;water-absorbing agent.
Solubility	Practically insoluble in acetone, chloroform, ethanol (95%), toluene, and ether. Insoluble in water, but swells to form a suspension.
Loss on drying	Not more than 10%
Density	0.52 g/cm3
Viscocity	5–2000 mPa s
Stability and Storage Conditions	Carboxymethylcellulose calcium is a stable, though hygroscopic material. It should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Carboxymethylcellulose sodium is incompatible with strongly acidic solutions and with the soluble salts of iron and some other metals, such as aluminum, mercury, and zinc. It is also incompatible with xanthan gum. Precipitation may occur at pH < 2, and also when it is mixed with ethanol (95%).
Applications	Carboxymethylcellulose sodium is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity-increasing properties. Higher concentrations, usually 3–6%, of the medium-viscosity grade are used to produce gels that can be used as the base for applications and pastes

5. 2 .3. Sodium Bicarbonate [34-35]

Synonyms	Baking soda; E500; Effer-Soda; monosodium carbonate; natrii hydrogenocarbonas; Sal de Vichy
Chemical Name	Carbonic acid monosodium salt
Molecular Weight	84.01
Functional Category	Alkalizing agent; therapeutic agent.
Loss on drying	Not more than 0.25%
Density (bulk)	0.869 g/cm3
Solubility	Ethanol (95%): Practically insoluble

	Ether : Practically insoluble Water : 1 in 11 1 in 4 at 100^0C(a) 1 in 10 at 25^0C 1 in 12 at 18^0C
Stability and storage	At ambient temperatures, aqueous solutions slowly decompose with partial conversion into the carbonate; the decomposition is accelerated by agitation or heat. Aqueous solutions of sodium bicarbonate stored in glass containers may develop deposits of small glass particles. Sediments of calcium carbonate with traces of magnesium or other metal carbonates have been found in injections sterilized by autoclaving; these are due to impurities in the bicarbonate or to extraction of calcium and magnesium ions from the glass container. Sedimentation may be retarded by the inclusion of 0.01–0.02% disodium edetate. Sodium bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in a well-closed container in a cool, dry place.
Incompatibility	Sodium bicarbonate reacts with acids, acidic salts, and many alkaloidal salts, with the evolution of carbon dioxide. Sodium bicarbonate can also intensify the darkening of salicylates.
Application	Recently, sodium bicarbonate has been used as a gas-forming agent in alginate raft systems and in floating, controlled release oral dosage forms for a range of drugs. Therapeutically, sodium bicarbonate may be used as an antacid, and as a source of the bicarbonate anion in the treatment of metabolic acidosis. Sodium bicarbonate may also be used as a component of oral rehydration salts and as a source of bicarbonate in dialysis fluids.

5 .2.4 Citric Acid Monohydrate [36-37]

Synonym	Acidum citricum monohydricum, 2-hydroxypropane-1,2,3-tricarboxylic acid monohydrate
Chemical Name	2-Hydroxy-1,2,3-propanetricarboxylicacid monohydrate

Molecular Weight	210.14
Functional Category	Acidifying agent; antioxidant; buffering agent; chelating agent;flavor enhancer; preservative
Density	1.542 g/cm3
Solubility	Soluble 1 in 1.5 parts of ethanol (95%) and 1 in less than 1 part of water; sparingly soluble in ether.
Stability and Storage Conditions	Citric acid monohydrate loses water of crystallization in dry air or when heated to about 40^0C. It is slightly deliquescent in moist air. Dilute aqueous solutions of citric acid may ferment on standing. The bulk monohydrate or anhydrous material should be stored in airtight containers in a cool, dry place
Incompatibilities	Citric acid is incompatible with potassium tartrate, alkali and alkaline earth carbonates and bicarbonates, acetates, and sulfides. Incompatibilities also include oxidizing agents, bases, reducing agents, and nitrates. It is potentially explosive in combination with metal nitrates. On storage, sucrose may crystallize from syrups in the presence of citric acid.
Applications	primarily to adjust the pH of solutions. It has also been used experimentally to adjust the pH of tablet matrices in enteric-coated formulations for colon-specific drug delivery. Citric acid monohydrate is used in the preparation of effervescent granules, while anhydrous citric acid is widely used in the preparation of effervescent tablets. Citric acid has also been shown to improve the stability of spray-dried insulin powder in inhalation formulations. In food products, citric acid is used as a flavor enhancer for its tart, acidic taste. Citric acid monohydrate is used as a sequestering agent and antioxidant synergist. It is also a component of anticoagulant citrate solutions. Therapeutically, preparations containing citric acid have been used to dissolve renal calculi.

5.2.5 Lactose monohydrate [38-39]

Synonyms	lactosum monohydricum; Monohydrate; Pharmatose; PrismaLac; SacheLac; SorboLac; SpheroLac; SuperTab 30GR; Tablettose
Chemical Name	O-b-D-Galactopyranosyl-(1,4)-a-D-glucopyranose monohydrate
Molecular weight	360.31
Loss on drying	Less than 0.5%
Density (true)	1.545 g/cm^3
Functional Category	Dry powder inhaler carrier; lyophilization aid; tablet binder; tablet and capsule diluent; tablet and capsule filler
Solubility	Chloroform : Practically insoluble Ethanol : Practically insoluble Ether : Practically insoluble Water : 1 in 5.24 1 in 3.05 at 40^{0}C 1 in 2.30 at 50^{0}C 1 in 1.71 at 60^{0}C
Stability and Storage Conditions	Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. The purities of different lactoses can vary and color evaluation may be important, particularly if white tablets are being formulated.
Incompatibilities	A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. The Maillard interaction has also been shown to occur between lactose and secondary amine. However, the reaction sequence stops with the formation of the imine, and no yellow-brown coloration develops.
Applications	Lactose is widely used as a filler and diluent in tablets and capsules, and also used as a diluent in dry-powder inhalation.

5.2.6 Magnesium Stearate [40-41]

Synonyms	Dibasic magnesium stearate; magnesium distearate; magnesia stearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid,
Chemical Name	Octadecanoic acid magnesium salt
Molecular Weight	591.24
Density (true)	1.092 g/cm3
Loss on drying	Not more than 6%
Functional Category	Tablet and capsule lubricant
Solubility	Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).
Stability and Storage Conditions	Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.
Application	Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

5.2.7 Microcrystalline cellulose [42-43]

Synonyms	Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose
Functional Category.	Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant
Loss on drying	Not more than 7%
Density (true)	1.512–1.668 g/cm3
Solubility	Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.
Stability and Storage Conditions	Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place
Incompatibilities.	Microcrystalline cellulose is incompatible with strong oxidizing agents
Applications	Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting

5.2.8. Polacrilin potassium (KYRONT-314) [44]

Synonyms	Amberlite IRP-88; methacrylic acid polymer with

	divinylbenzene,potassium salt; polacrilinum kalii.
Chemical Name	2-Methyl-2-propenoic acid polymer with divinylbenzene, potassium salt
Functional Category	Tablet and capsule disintegrant
Description	Polacrilin potassium occurs as a cream-colored, odorless and tasteless, free-flowing powder. Aqueous dispersions have a bitter taste.
Loss on Drying	Not more than 10%
Density	0.48 g/cm^3
Solubility	practically insoluble in water and most other liquids, although polacrilin resins swell rapidly when wetted.
Stability and Storage Conditions	Polacrilin potassium and other polacrilin resins are stable to light, air, and heat up to their maximum operation temperature;see Table II. Excessive heating can cause thermal decomposition of the resins and may yield one or more oxides of carbon, nitrogen, sulfur, and/or amines.
Applications	Polacrilin potassium is a cation-exchange resin used in oral pharmaceutical formulations as a tablet disintegrant. Concentrations of 2–10% w/w have been used for this purpose although 2% w/w of polacrilin potassium is usually sufficient.Other polacrilin ion-exchange resins have been used as excipients to stabilize drugs, to mask or modify the taste of drugs, and in the preparation of sustained-release dosage forms and drug carriers. Polacrilin resins are also used in the analysis and manufacture of pharmaceuticals and food products.

5.2.9. Croscarmellose sodium [45-46]

Synonyms	*Ac-Di-Sol*; crosslinked carboxymethylcellulose sodium; *Explocel*; modified cellulose gum;*Nymcel ZSX*; *Pharmacel XL*; *Primellose*; *Solutab*; *Vivasol*.
Chemical Name	Cellulose, carboxymethyl ether, sodium salt
Functional Category	Tablet and capsule disintegrant.

Solubility	insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.
Density	1.543 g/cm3
Stability and Storage Conditions	Croscarmellose sodium is a stable though hygroscopic material.A model tablet formulation prepared by direct compression, with CCS as a disintegrant, showed no significant difference in drug dissolution after storage at 30°C for 14 months.
Incompatibilities	The efficacy of disintegrants, such as CCS, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol CCS is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

6. EXPERIMENTAL WORK

6.1 SPECTROSCOPIC CHARACTERIZATION OF NIFIDEPINE:

6.1.1 UV Spectroscopy

6.1.1.1 Determination of λ_{max}

Nifidepine (10mg) was accurately weighed and dissolved in 0.1 N HCl in 100ml of volumetric flask and final volume was adjusted to 100ml. The stock solution (100µg/ml) was further diluted using distilled water to get serial dilutions (5 to 50 µg/ml).The solution was kept in a fused silica cuvette. The UV spectrum was recorded in the range of 200-400 nm on UB Varian Cary 100 scan double beam UV visible spectrophotometer at 1 cm, slit width. The spectrum and wavelength of maximum absorption were recorded.

6.1.1.2. Preparation of Standard Curve:

Standard curves were prepared by dissolving 10mg nifidepine in 100ml of 0.1 N HCl. The stock solution (100µg/ml) was further diluted with the same to get solutions in concentration range of 5 to 50 µg/ml. The absorbance of these solutions was determined spectrophotometrically at 236 nm and Beer's Lamberts graph was plotted using absorbance concentration data.

6.1.2. FTIR Spectrum interpretation[12]

The dry sample of nifidepine was mixed and triturated with dry potassium bromide. The KBr discs were prepared by compressing the powders at pressure of 5 tons for 5 min. in a hydraulic press. Scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 600 cm^{-1}

6.2 Physicochemical parameters of the A.P.I. [47-48]

6.2.1 Bulk Density

Accurately weighed 25 g of test sample (Candidate drug) was taken and sifted through #18 and transferred it to 100 ml graduated measuring cylinder. The volume of mass (M) observed without compacting. Then unsettled apparent volume (V_0) level was noted. The bulk density (ρ_b) was calculated by following formula

$$\rho_b = M / V_0$$

6.2.2 Tapped Density

Accurately weighed 25 gm of candidate drug was screened through #18 and transferred to a 100 ml graduated measuring cylinder without compacting. The cylinder was placed on the USP tapped density tester and was mechanically tapped, allowing it to drop under its own weight that provides a fixed drop from 14 ± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped for 500 times initially and tapped volume V_1 was measured to nearest graduated units. The cylinder was tapped repeatedly for additional tapping for 750 times and tapped volume V_2 was noted to the nearest graduated unit. If the difference between the two volumes (V_1 and V_2) is more than 2% then repeated tapping for 1250 times and tapped volume (V_t) was noted. The tapped density (ρ_t) was calculated by formula

$$\rho = M / Vt$$

Where, – M- Mass of powder

6.2.3 Compressibility index

The compressibility index is measure of the capacity of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In a free flowing powder, such interactions are generally less significant, and the bulk and tapped densities are closer in value. For poor flowing materials, there are frequently greater inter-particulate interactions, and a greater difference between the bulk and tapped densities are observed.

Table No.6.1 Scale of flowability-by CI

Sr.No.	Compressibility index (%)	Flow characteristic
1.	< 10	Excellent
2.	11-15	Good
3.	16-20	Fair
4.	21-25	Passable
5.	26-31	Poor
6.	32-37	Very poor
7.	>38	Very very poor

The compressibility index is calculated as follows:

$$\textbf{Compressibility Index} = \frac{V_0 - V_t}{V_0} \times 100$$

Where,

V_o = Bulk volume

V_t = Tapped volume.

6.2.4 Hausner's Ratio (H)

This is an indirect index of ease of powder flow. Hausner's Ratio is an indication of flowability of a powder.

Table 6.2 Scale of flowability-by HR

Sr.No.	Hausner's ratio	Flow characteristic
1.	1.00-1.11	Excellent
2.	1.12-1.18	Good
3.	1.19-1.25	Fair
4.	1.26-1.34	Passable
5.	1.35-1.45	Poor
6.	1.46-1.59	Very poor
7.	>1.60	Very very poor

It is calculated by the following formula,

$$\textbf{Hausner's ratio} = \frac{V_0}{V_t}$$

Where, V_o - Bulk volume

V_t - Tapped volume

6.3 Compatibility Study by DSC

Five milligram of drug sample was accurately weighed and placed in the hermetic aluminum DSC pan. The pan was sealed with the help of hydraulic press. The sample was heated in DSC furnace for programmed temperature range 50 to 300ºC at heating rate of 0.5ºC/min. The nitrogen flux rate was set at 20 mL/min. The study was performed using DSC6 instrument (Perkin Elmer, Germany). DSC studies of nifidepine were carried out with each excipient.

Table no. 6.3 Drug-Excipients Compatibility Study

	Storage		
	40°C/75% RH 1 M open	40°C/75% RH 1 M closed	55°C 1 M open
Nifidepine	Alone	Alone	Alone
Croscsrmalose sodium +Nifidepine	(1:1)	(1:1)	(1:1)
Kyron t 314+Nifidepine	(1:1)	(1:1)	(1:1)
Magnesium stearate+Nifidepine	(1:1)	(1:1)	(1:1)
Lactose+Nifidepine	(1:1)	(1:1)	(1:1)
Hpmc k4m+Nifidepine	(1:1)	(1:1)	(1:1)
Hpmc e 15 lv+Nifidepine	(1:1)	(1:1)	(1:1)
Hpmc k 100+Nifidepine	(1:1)	(1:1)	(1:1)
Sodium bicarbonate+Nifidepine	(1:1)	(1:1)	(1:1)
Citric acid+Nifidepine	(1:1)	(1:1)	(1:1)
Di calcium phosphate+Nifidepine	(1:1)	(1:1)	(1:1)
Microcrystsline celllose+Nifidepine	(1:1)	(1:1)	(1:1)

nifidepine was mixed with 1:1 proportion with all excipients to be used in our formulation. and kept at 40°C/75% RH (close), 55°C (close), 55°C (open) for one month. Thermograms were obtained after a month by DSC study confirmed the compatibility of the excipients with the A.P.I.

6.4 PHYSICOCHEMICAL PARAMETERS OF POWDER BLEND[47]

6.4.1 Particle size analysis of powder blend by Sieving method

This test was performed with the help of sieves of different size. They were fitted in the platform of sieve shaker in such a way that the coarse sieve was placed on top corresponding to the finer sieves. Placed 50 gm sample on the top and run the machine for 5 min. and took the weight of the retention on the sieve(s).Finally calculated the % of retention on each sieve by the following equation.

$$\% \text{ retained} = \frac{\text{quantity of retention}}{50} X100$$

6.4.2 Bulk density of powder blend

A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent

volume, Vo, to the nearest graduated unit. Calculate the bulk density, in gm per ml, by the formula

Bulk density = Bulk Mass/ Bulk Volume

6.4.3 Tapped density of powder blend

After observing the initial volume, the cylinder is mechanically tapped and volume readings are taken until little further volume changes observed. Cylinder dropping distance: 14± 2 mm at a normal rate of 300 drops / minute. Unless otherwise specified, tap the cylinder 500 times initially and measure the tapped volume, VA, to the nearest graduated unit. Repeat the tapping an additional 750 times and measure the tapped volume, Vb, to the nearest graduated unit. If the difference between the two volumes is less than 2%, Vb is the final tapped volume, Vf. Repeat in increments of 1250 taps, as needed, unit the difference between succeeding measurements is less than 2%. Calculate the tapped density, in gm per ml, by the formula

$$\text{Tapped Density} = \frac{m}{Vf}$$

6.4.4 Measurement of Powder Compressibility

The compressibility index and Hausner's ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free flowing power, such interactions are generally less and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the compressibility Index and the Hausner's ratio calculated by the formula

$$\text{Compressibility index: } = 100\,\frac{(V_0 - Vf)}{V_0}$$

$$\text{Hausner's Ratio: } = \frac{V_0}{Vf}$$

6.4.5 Loss on drying

Crush the tablet with the help of mortar and pestle. Take crucible and keep in drying oven at 105°C for half an hour. Cool at room temperature in a desiccator for 30 minutes. Weigh accurately empty bottle, add 2 g of powder into it and weigh. Distribute the sample as evenly as practicable by gentle sidewise shaking to a depth

not exceeding 10 mm. Place the LOD bottle in the drying oven at 105°c by for four hours. After drying is completed, open the drying oven, close the crucible carefully and allow it to cool at room temperature in desiccator for 30 minutes. Weigh the crucible and calculate the percentage LOD.

Calculation

Wt. of empty crucible (W1)

Wt. of crucible + sample (W2)

Wt. of sample (W2-W1)

Wt. of crucible + sample after drying (W3)

Loss in wt. of sample after drying (W2-W3):

$$\text{LOD (\% w/w)} = \frac{(W2 - W3)}{(W2 - W1)} \times 100$$

6.5 FORMULATION AND DEVELOPMENT OF FLOATING PULSATILE DRUG DELIVERY SYSTEM OF NIFIDEPINE [11]

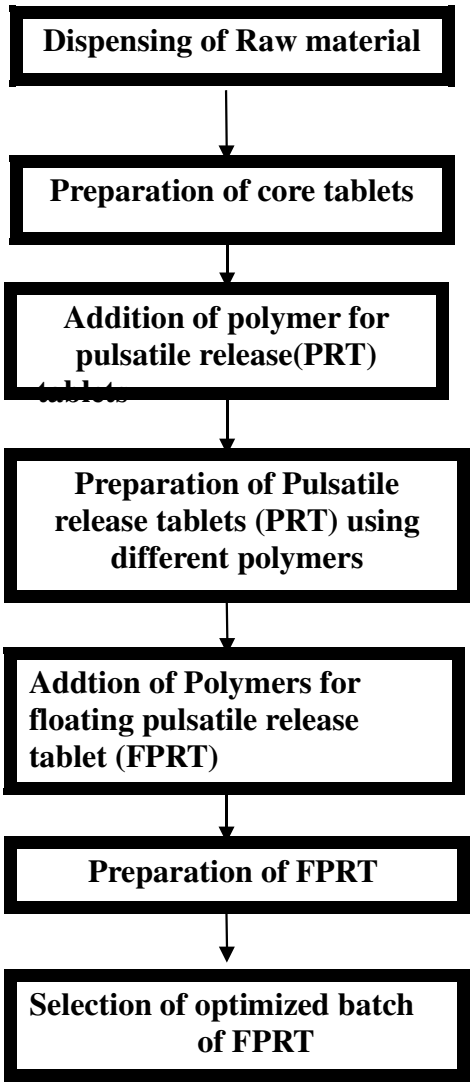


Fig 6.1: Process Flow Chart

6.5.1 Preparation of the Rapid Release Tablet (RRT) [11]

The inner core tablets were prepared by using direct compression method. Different preliminary batches of core tablets were taken in to fix concentration of superdisintegrant in tablet. Concentration of super disintegrants varies from 1 to 4 mg/tablet. Powder mixtures of nifidepine, crosscarmellose sodium (Ac-Di-Sol), KYRON T314, lactose and ingredients were dry blended for 20 min. followed by addition of magnesium stearate. The mixtures were then further blended for 10 min, 60 mg of resultant powder blend (theoretically equivalent to 20 mg of nifidepine) was compressed using rotary tabletting machine (Cadmach Machinery, Ahmedabad, India) with a 6mm punch and die to obtain the core tablet.

Table 6.4: Formulations of core tablet

Ingredients (mg)	**I**	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**
Nifidepine (mg)	20	20	20	20	20	20	20	20
CCS(mg)	1	2	3	4	-	-	-	-
KYRON T 314(mg)	-	-	-	-	1	2	3	4
Mg-Stearate(mg)	8	8	8	8	8	8	8	8
Lactose(mg)	31	30	29	28	31	30	29	28
TOTAL (mg)	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**

Evaluation of the Rapid Release Tablet (RRT)

Determination of Drug Content

Total 10 tablet were weighed and powder equivalent to 25 mg of Nifidepine was weighed and dissolved in methanol then filtered through Whatman filter paper. Solution was analysed for content by UV-Spectrophotometer at 236 nm using methanol as blank.

Disintegration test

The tablet was put into 100 ml distilled water at 37 ± 2°C. Time required for complete dispersion of a tablet was measured with the help of a digital tablet disintegration test apparatus.

Hardness test

Pfizer hardness tester was used for the determination of hardness of tablets. The tablet was placed in contact between the plungers and handle was pressed. The force of fractured was recorded.

Friability test

The friability of all the tablets studied was determined using a Roche friabilator. In the disinteration time study,

From above study two batches II and VI were selected as optimized batches.

6.5.2 Preparation of the Floating and Pulsatile Release Tablet (FPRT) [11]

FPRT was designed to comprise PRT and top cover buoyant layer. PRT was taken as the layer for pulsatile release.

6.5.2.1 Preparation of the Pulsatile Release Tablet (PRT)

Each powder used as erodible outer shell i.e. HPMC K4, HPMC E15 LV, carboxy methylcellulose sodium (NaCMC) was passed through a 500µm. RRT was taken as core. Studies were carried out on different combination of polymers, which were considered as preliminary batches. Dissolution study was carried out for above batches and by observing result it was necessary to carry out experiment on individual polymers.

Table 6.5: Addition of polymer for pulsatile release tablet containing crosscarmellose sodium

Sr No.	Ingredients	Formulation Codes								
		C1	C2	C3	C4	C5	C6	C7	C8	C9
1	HPMC K4 M	140	160	180	-	-	-	-	-	-
2	NaCMC	-	-	-	140	160	180	-	-	-
3	HPMCE15 LV	-	-	-	-	-	-	230	260	290

Table 6.6: Addition of polymer for pulsatile release tablet containing KYRON T314

	Ingredients	Formulation Codes

		K1	K2	K3	K4	K5	K6
1	HPMC K4 M	140	160	180	-	-	-
2	HPMCE15 LV	-	-	-	230	260	290

For HPMC K4, 60 mg of powder was filled in a die followed by RRT in the center of die. Slightly pressed the tablet to fix the coatings around and under the core, then the rest of the coatings was filled and compressed. Same procedure was applied to rest of the powders i.e. for HPMC E15LV and NaCMC. For the above batches dissolution study was conducted from which optimized batches were selected and only that batches were conducted for further study.

6.5.2.2 Compositions of the Buoyant Layers

The compositions of the buoyant layer of the FPRT for floating testing were shown in Table 6.8. All powdered excipients were mixed for 5 min using a mortar and pestle to form a homogenous directly compressible powder mix. Different fillers were used to adjust the tablet weight and effect of fillers on floating time was observed.
For the preparation of FPRT tablet, batch K3 and K6 were used in compression with buoyant layer.

Table 6.7: Compositions of the Buoyant Layers

Sr No.	Ingredients	Formulation codes				
		F1	F2	F3	F4	F5
1	HPMC K 100M	150	150	150	150	150
2	Sodium bicarbonate	20	40	80	40	20
3	Citric acid	20	40	80	40	20
4	Dicalcium phosphate	20	-	-	-	-
5	Microcrystalline cellulose	-	20	-	-	-
6	Lactose	-	-	20	20	20

6.6 EVALUATION OF FLOATING AND PULSATILE RELEASE TABLET [47-48]

6.6.1 Physical evaluation

6.6.1.1 Friability test

The friability of all the tablets studied was determined using a Roche friabilator.

6.6.1.2 Hardness test:

Pfizer hardness tester was used for the determination of hardness of tablets.The tablet was placed in contact between the plungers and handle was pressed.The force of fractured was recorded.

6.6.1.4 Determination of Drug Content:

Total 10 tablet were weighed and powder equivalent to 20 mg of nifidepine was weighed and dissolved in methanol then filtered through Whatman filter paper. Solution was analysed for nifidepine content by UV Spectrophotometer at 236 nm using methanol as blank

6.6.1.5 In Vitro Buoyancy Determination [11]

Floating behavior of the tablet is determined by using USP dissolution apparatus II in 500 ml of 0.1 N HCl which is maintained at 37±0.5°C, rotated at 50 rpm. The floating lag time as well as total floating time is observed.

6.6.1.6 Swelling Index determination

Tablets were weighed individually (designated as W1) and placed separately in glass beaker containing 200 ml of 0.1 N HCl and incubated at 37°C±1°C. At regular 1-h time intervals until 24 h, the tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then re-weighed (W2) and swelling index (SI) was calculated using the following formula:

$$SI = \frac{W2-W1}{W1} \times 100 \quad \text{---------- (6.1)}$$

6.7 DISSOLUTION STUDIES [11]

Parameters

Dissolution media	-0.1 N HCl,
Volume of Dissolution medium	- 900 ml,
RPM	- 50,
Temperature of dissolution mediu	- 37.0 ± 0.5^{0}C,
Apparatus type	- USP Apparatus II.

A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 15 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 236 nm

using Varian cary-100 double beam UV spectroscopy. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

6.8 STABILITY TESTING OF THE OPTIMIZED FORMULATION

Temperature dependent stability studies were carried out on the optimized batch. They were packed in low density polyethylene (LDPE) bags enclose in high density polyethylene (HDPE) container and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(I) 30 $\pm$ 2 °C and RH 65 % $\pm$ 5%

(II) 40 $\pm$ 2 °C and RH 75 % $\pm$ 5%

Tablets were withdrawn after a period of 7, 14 days, 1, 2, 3 months and analyzed for physical characterization (appearance, moisture content), dissolution study and percentage assay.

6.9 DRUG RELEASE MECHANISM FROM MATRICES [49-51]

The mechanism of drug release has been proposed that drug release from the matrices usually implies water penetration in the matrix, hydration, swelling, diffusion of the dissolved drug (polymer hydro fusion), and or the erosion of the gelatinous layer. However, it is worth mention that the release mechanism of a drug would depend on the dosage form selected, pH, and nature of the drug and, of course, the polymer used.

6,9.1. Zero order kinetics

Drug dissolution from pharmaceutical dosage from that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation.

$$W_0 - W_t = Kt$$

Where, W_0 = initial amount of drug in the pharmaceutical dosage form,

W_t = amount of drug in the pharmaceutical dosage form,

t = time,

K = Proportionality constant.

The pharmaceutical dosage form following this profile release the same amount of drug by unit of time and in this model can be explained by following equation

$$Q_t = Q_0 + K_0 t$$

Where, Q_t = Drug dissolved in time t,

Q_0 = Initial amount of drug in solution,

K_0 = Zero order rate constant

6.9.2. First order kinetics

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967) and later by Wagner. The dissolution phenomena implies a surface action, as can be seen by Noyes–Whitney equation,

$$\frac{dc}{dt} = K(C_s - C)$$

Where, C = Concentration of solute in time t,

C_S = solubility in equilibrium at experience temperature.

k =First order proportionality constant

Hixson and Crowell adapted the above equation as

$$\frac{Dw}{dt} = KS(C_s - C)$$

Where, w = amount of solute in solution at time t,

S = Solid area accessible to dissolution.

$$\log Q_t = \log Q_0 + K_1.t / 2.303$$

Where, Q_t = amount of drug release in time t,

Q_0 = initial amount of drug in solution,

K_1 = First order release constant.

Above equation also represents this model.

The pharmaceutical dosage form following this dissolution profile, such as those containing water soluble drugs in porous matrices release drug in a way that is proportional to amount of drug remaining in its interior in such a way that amount of drug released by unit of time diminish.

6.9.3 Higuchi Model

Higuchi developed mathematical expressions for drugs particles dispersed in a uniform matrix behaving as diffusion media. To study the dissolution form a planar system having a homogeneous matrix, the relation obtained was

$$ft = Q = \sqrt{(2C - C_S)C_S t}$$

Where, Q = Amount of drug released in time t per unit area.

C = Drug initial concentration
C_S = drug solubility in matrix media
D = Diffusivity of drug molecules in matrix substance.

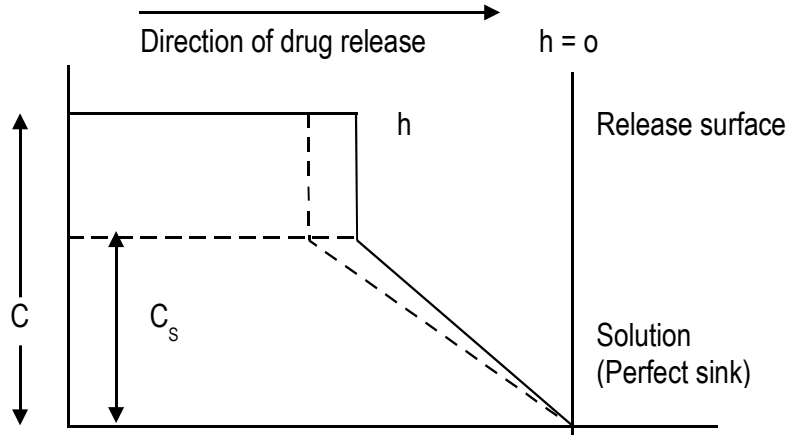


Fig.6.2: Drug theoretical concentration profile of a matrix system in direct contact with a perfect sink release media.

The solid line represents the variation of drug concentration in the pharmaceutical system after time t. To distance h, the concentration gradient will be constant, provided C>> Cs. The linearity order follows the Fick's law.

$$Q = \sqrt{tDC_S(2C - C_S)}$$

Relation is valid during all time except when the total depletion of drug in therapeutic system is achieved .Higuchi developed other models for release from heterogeneous matrix, when the drug concentration in matrix is lower than its solubility and the release occurs through pores in matrix, the obtained relation is:

$$\text{ft} = Q = \sqrt{\frac{DE}{T}(2C - \varepsilon C_S)C_S t}$$

6.9.4 Korsmeyer and peppas model

This equation is useful to study the diffusion / relaxation release of dosage form as well zero order release kinetics. The equation can be described as

$$\frac{M_t}{M\infty} = Kt^n$$

Where, $\frac{M_t}{M\infty}$ = fraction of drug release in time t,

K = constant incorporating structural and geometric characteristics of controlled release device.

n = diffusion release exponent indicative of release mechanism.

For release from swellable cylinders Ritger and Peppas have indicated,

n = 0.45 for Fickian diffusion,

n > 0 .45 and < 0.89 for anomalous diffusion or non Fickian diffusion (0.5 < n < 1)

n = 0.89 for zero order release

n = 1 or > 1 for super case

7. RESULTS AND DISCUSSION

7.1 CHARACTERIZATION AND PREPARATION OF CALIBRATION CURVE OF NIFEDIPINE

7.1.1 UV Spectroscopy

Determination of λ max and preparation of standard curve

The UV spectrum obtained is shown in Fig.7.1**.** The wavelength of maximum absorbance (λ max.) was found to be at 236 nm for 0.1 N HCl (Simulated gastric Fluid) solutions. Using absorbance-concentration data; calibration curve was plotted and is shown in Fig. 7.2. The plot of Absorbance v/s Concentration (µg/ml) was found to be linear in the concentration range of 0 to 50 µg/ml and obeys the Beer-Lambert's law in the same ranges.

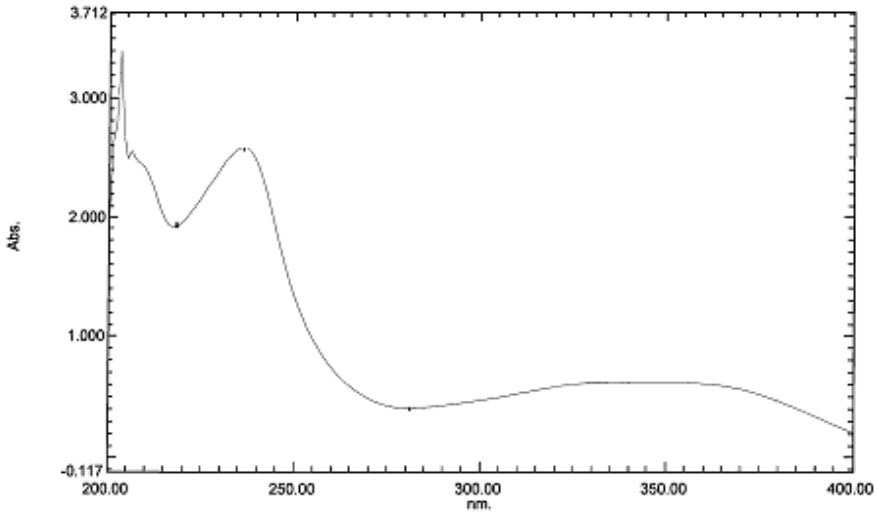


Fig 7.1:

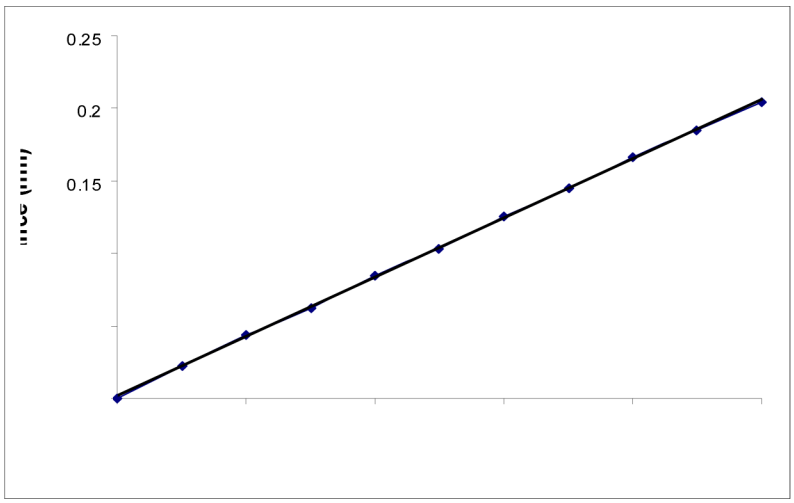


Fig. 7.2: Calibration Curve of Nifedipine

Parameters	Value
Beer's law limit (µg/ml)236 nm Wavelength of detection (nm)	0 – 50
Regression Equation (y = mx + c) [1]	
Slope (m)	
0.0041Intercept (c)	0.0015
Correlation coefficient	0.9997

where y is the absorbance and x is the concentration (µg/ml)

7.1.2 IR Spectrum Interpretation

The IR spectrum of Nifedipine is shown in **Figure. 7.3**

The interpretation of IR frequencies is done and shown in **Table 7.1**

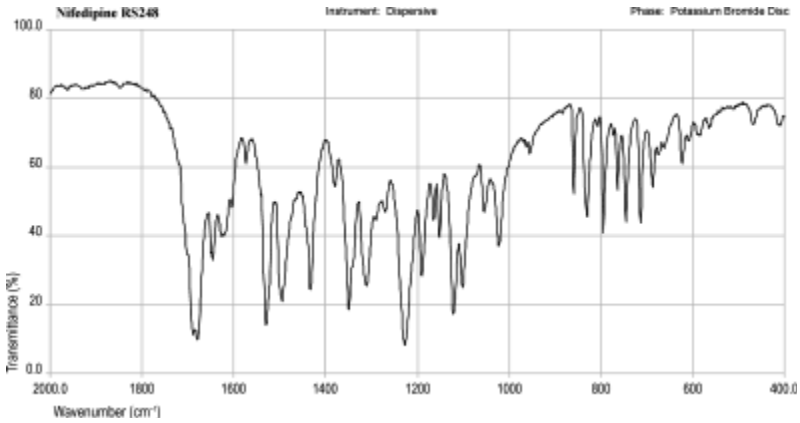


Fig.7.3: IR Spectrum of Nifedipine

Table 7.1: IR Spectrum of Nifedipine

Groups	Range (1/cm)
N-H	3325
C=O	1680
C=C	1650
NO_2	1530,1350
Aromatic ring	1515-1580

7.2 Physicochemical parameters of the A.P.I.

7.2.1 Physical characterization of candidate drug

Table No.7.2: Physical properties of candidate drug

Bulk density (g/ml)	0.235
Tapped density (g/ml)	0.423
Carr's index (%)	44.44
Hausner ratio	1.80

The data shows that nifedipine is poor flowing.

7.3 Compatibility Study by DSC

7.3.1 DSC analysis of pure nifedipine

The drug showed sharp endotherm at 172.41°C with starting at 172.14°C. The reported value is 172.5°C. The DSC thermo gram is presented in Figure No.7.4

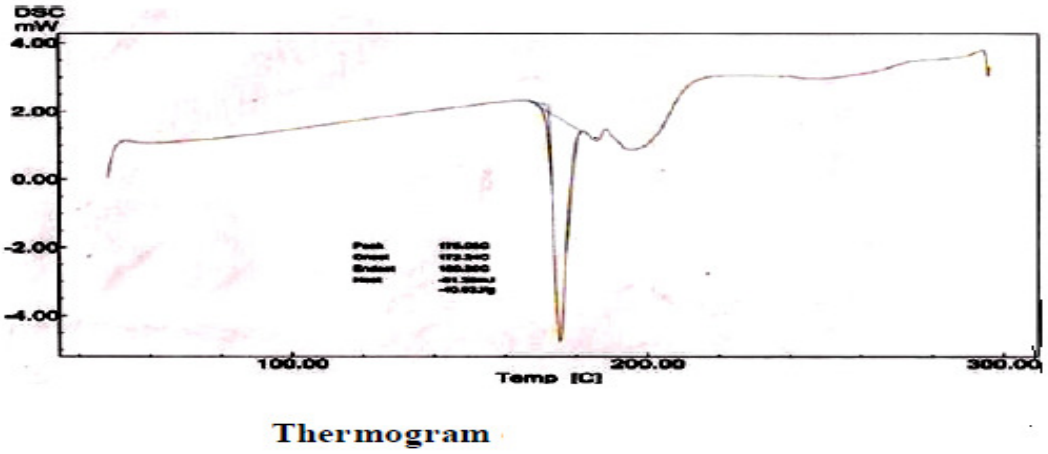


Figure No.7.4: DSC analysis of Nifedipine

7.3.2 The thermo gram obtained By The D.S.C technology with nifedipine and KYRON T 314

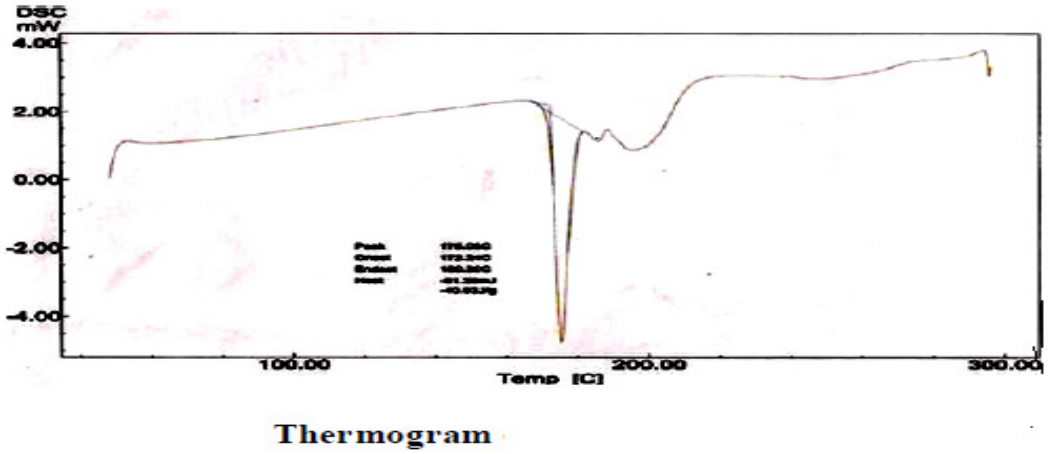


Fig no.7.5 Thermogram of nifedipin and KYRON T 314

No significant change is observed in melting point.

7.3.3 The thermo gram obtained By The D.S.C technology with nifedipine and croscsrmalose sodium

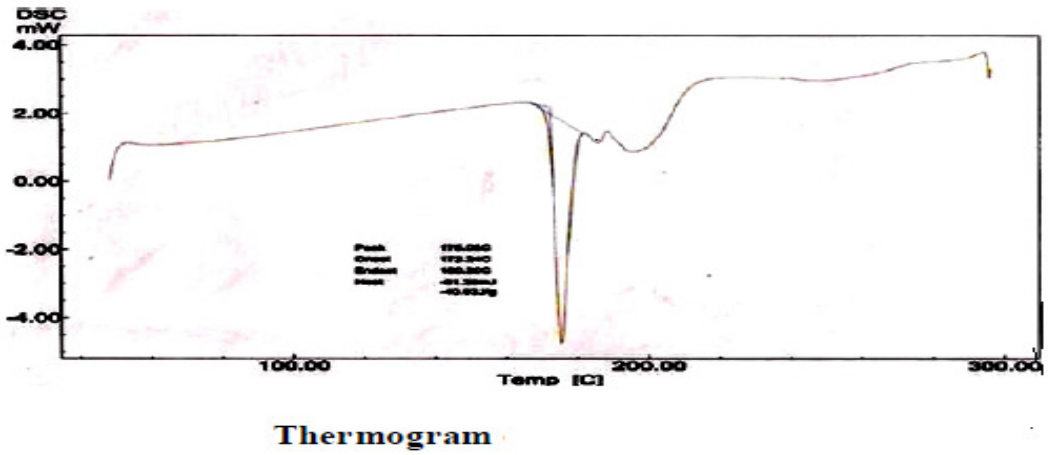


Fig no.7.6 Thermogram of nifedipine and croscarmellose sodium

No significant change is observed in melting point.

7.3.4 The thermo gram obtained By The D.S.C technology with nifedipine and magnesium stearate

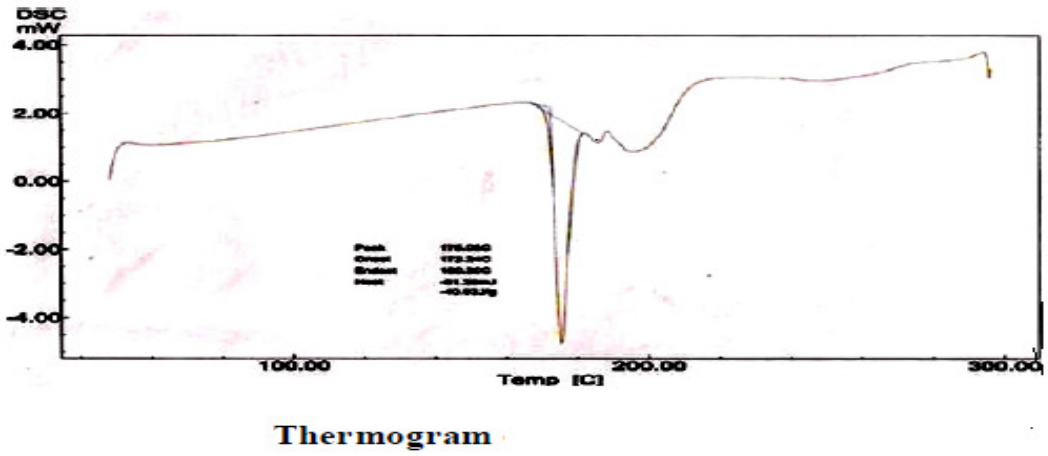


Fig no.7.7 Thermogram of nifedipine and magnesium stearate

No significant change is observed in melting point.

7.3.5 The thermo gram obtained By The D.S.C technology with nifedipine and lactose

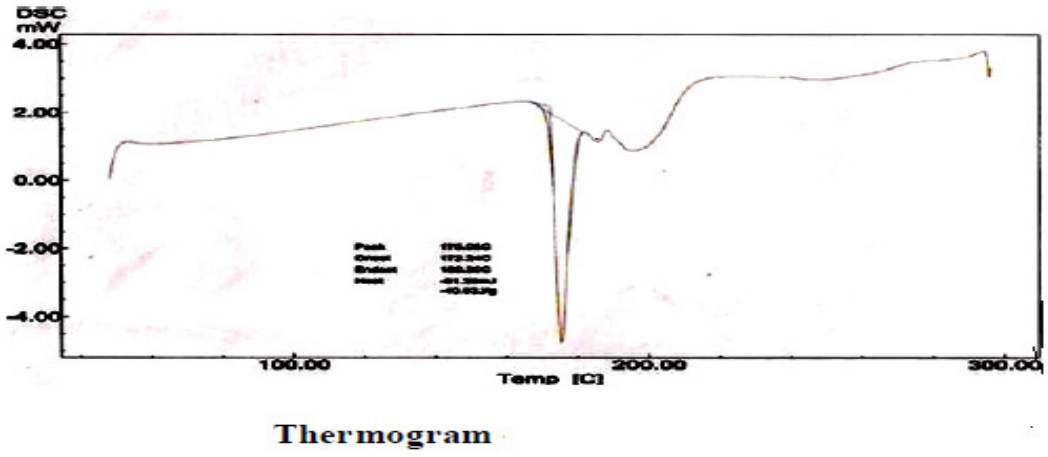


Fig no.7.8 Thermogram of nifedipine and lactose

No significant change is observed in melting point.

7.3.6 The thermo gram obtained By The D.S.C technology with nifedipine and HPMC K 4M

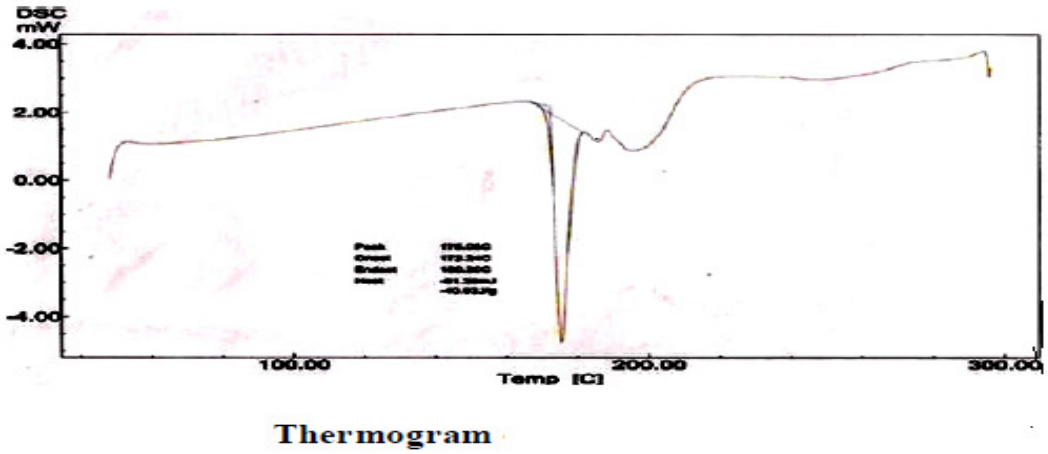


Fig no.7.9 Thermogram of nifedipine and HPMC K 4M

No significant change is observed in melting point.

7.3.7 The thermo gram obtained By The D.S.C technology with nifedipine and HPMC E 15 LV

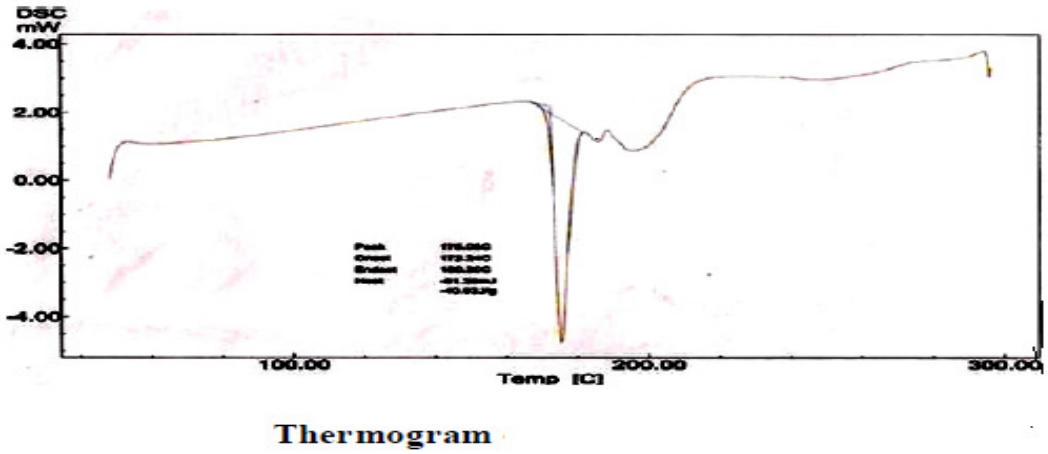


Fig no.7.10 The thermo gram obtained By The D.S.C technology with nifedipine and HPMC E 15 L

No significant change is observed in melting point.

7.3.8 The thermo gram obtained By The D.S.C technology with nifedipine and HPMC K 100

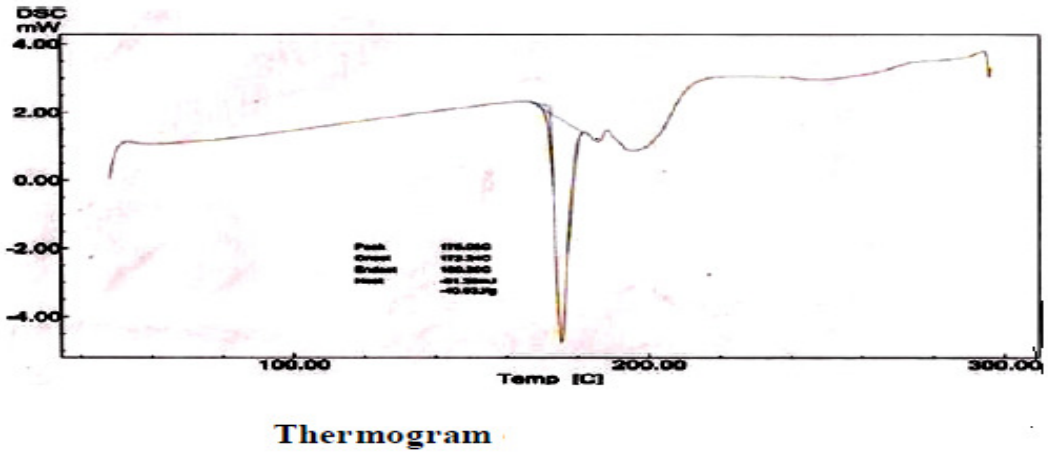


Fig no.7.11 The thermo gram obtained By The D.S.C technology with nifedipine and HPMC K 100

No significant change is observed in melting point.

7.3.9 The thermo gram obtained By The D.S.C technology with nifedipine and sodium bicarbonate

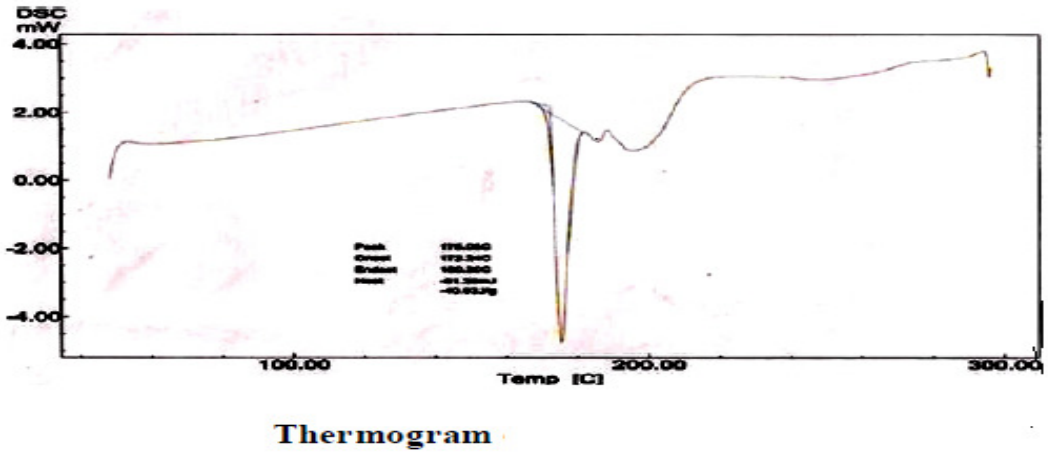


Fig no.7.12 The thermo gram obtained By The D.S.C technology with nifedipine and sodium bicarbonate

No significant change is observed in melting point.

7.3.10 The thermo gram obtained By The D.S.C technology with nifedipine and citric acid

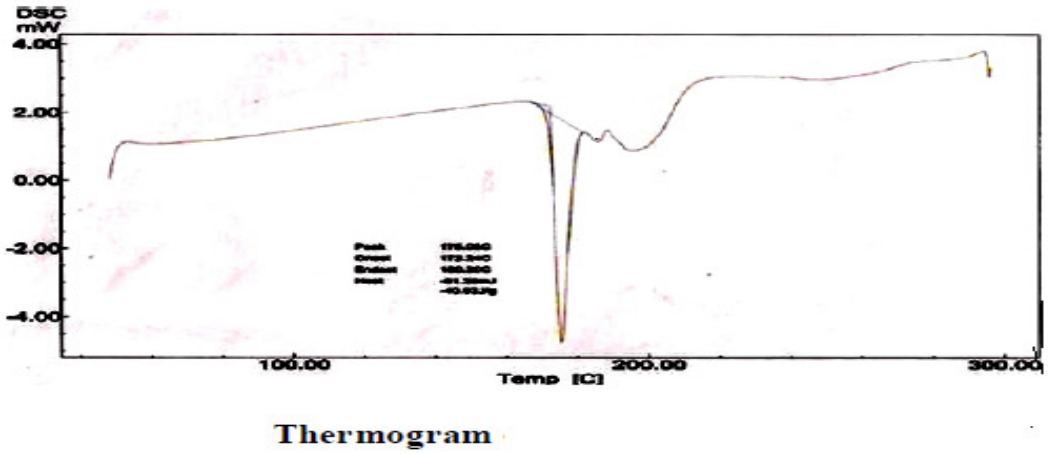


Fig no.7.13 The thermo gram obtained By The D.S.C technology with nifedipine and citric acid

No significant change is observed in melting point**.**

7.3.11 The thermo gram obtained By The D.S.C technology with nifedipine and di calcium phosphate

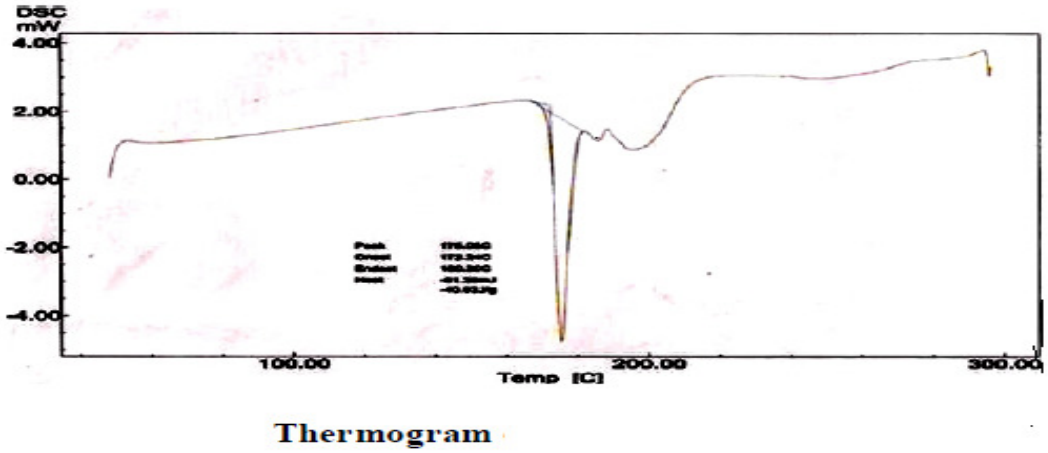
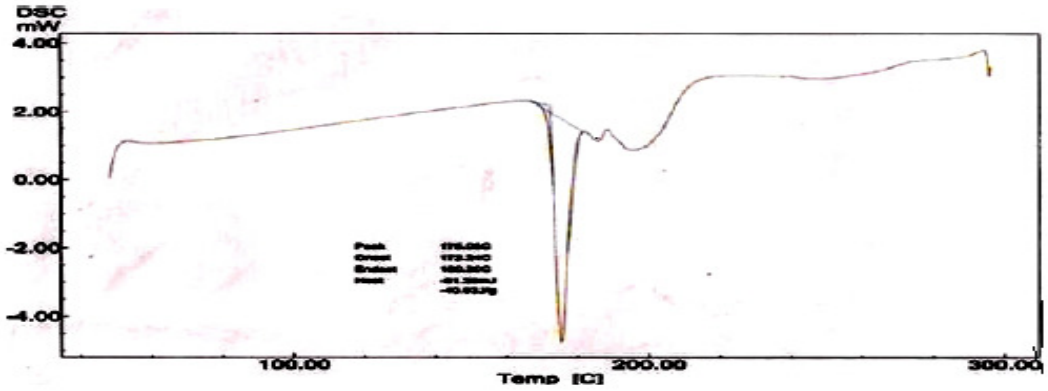


Fig no.7.14 Thermogram of nifedipine and di calcium phophate

No significant change is observed in melting point.

7.3.12 The thermo gram obtained By The D.S.C technology with nifedipine and Microcrystaline cellulose



Thermogram

Fig no.7.15 Thermogram of nifedipine and microcrystalline cellulose

No significant change is observed in melting point.

7.4 PHYSICOCHEMICAL PARAMETERS OF POWDER BLEND

7.4.1 Particle size analysis of powder blend by Sieving method

Particle size distribution (PSD) of granules was performed using sieve analysis with different mesh size.

Table 7.3: Particle size Distribution data lubricated granules

Trial No.	Cumulative percent sample retained (%)					
	30 #	40#	60#	80#	100#	Collector
1	47.52	64.84	75.72	88.44	92.36	100.00
2	16.42	32.405	45.64	60.45	70.73	100.00
3	31.20	75.64	75.68	76.48	85.64	100.00
4	16.40	32.40	45.64	60.44	70.76	100.00
5	40.52	58.54	65.55	81.20	91 35	100.00
6	35.21	80. 20	81.56	86.23	94.23	100.00
7	8.16	35.56	92.28	92.32	92.44	100.00
8	05.23	38.23	55.44	79.04	92.68	100.00

7.4 Analysis of powder blend for density and LOD

Trial No.	LOD (%L)	Granules			
		Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index	Hausner's ratio
1	0.65	0.440	0.480	8.33	1.09
2	0.68	0.467	0.565	17.39	1.11
3	0.68	0.510	0.520	13.95	0.98
4	0.68	0.456	0.543	16.03	1.19
5	0.58	0.446	0.536	16.79	1.20
6	0.68	0.456	0.543	16.03	1.19
7	0.68	0.456	0.521	12.26	1.14
8	0.86	0.456	0.543	16.03	1.19

7.5 EVALUATION OF RAPID RELEASE TABLET (RRT)

Table 7.5: Evaluation of RRT

Formulation	Hardness Kg/cm^2	Friability (%)	Drug Content (mg%)	Disintegration Time(S)
I	3.8	0.62±0.12	99.22	45
II	3.4	0.69±0.14	98.92	11
III	3.7	0.65±0.11	99.85	30
IV	3.8	0.62±0.11	99.72	28
V	3.6	0.60±0.14	99.35	24
VI	3.2	0.67±0.13	99.97	11
VII	3.9	0.63±0.16	99.65	49
VIII	3.6	0.60±0.11	99.78	10.4

In all formulation, the hardness test indicated good mechanical strength, whereas friability is less than 1% which indicated that tablet had good mechanical resistance.Drug content was found to be high (>99.20) and uniform in all tablet formulations. It was ranged from 98.92 to 99.85 and uniform in all tablet formulations. Absorption maxima was determined by scanning different concentration of solution of drug Nifedipine. Absorption maxima was 236 nm and method obeys Beer's law in concentration range 0 to 50 µg/ml, with good correlation coefficient (0.9997).When a standard drug solution was assayed repeatedly (n=6),relative error

(accuracy) and relative standard deviation (precision) were found to be 0.72 and 0.93 % respectively. The tablets were subjected for evaluation of the in-vitro disintegration time and it was observed that the time for formulation varied from 10 to 52 second. It was observed that the time for formulation varied from 10 to 52 second. It was observed that when KYRON T314 was used as disintegrant, tablet was disintegrate within short time due to easy and high swelling ability of KYRON T314 as compared to CCS. It is observed that disintegration time of tablet decreased with increased in concentration of CCS and KYRON T-314. But by disintegration study it was observed that hardness plays important role. For development of pulsatile release study disintegration time must be short to obtain burst effect therefore having less hardness. Hence by observing results it was concluded that batches II and VI were optimized batches which was confirmed by dissolution study.

7.5.1 Dissolution Study Of Rapid Release Tablet (RRT)

Table 7.6: Dissolution testing of Batch I-IV

Time (min)	% Drug Release			
	I	**II**	**III**	**IV**
0	0	0	0	0
1	48.84	49.23	53.43	54.78
2	55.67	57.87	62.49	65.98
3	63.87	66.9	69.45	70.1
4	68.93	70.92	74.82	76.9
5	77.68	79.99	82.56	83.76
6	83.56	86.79	88.93	89.92
7	88.94	90.56	92.39	93.44
8	94.69	97.84	98.7	99.45
9	98.95	98.9	99.28	
10	99.87	99.99	100.09	

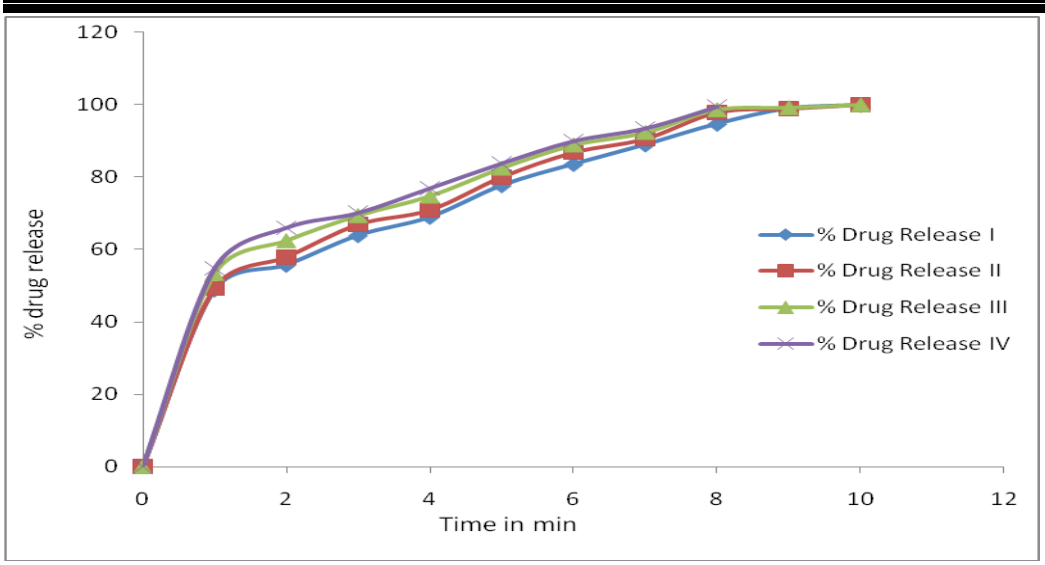


Fig 7.16: Dissolution testing of Batch I-IV

Table 7.7: Dissolution Testing of batch V-VIII

Time (min)	% Drug Release			
	V	VI	VII	VIII
0	0	0	0	0
1	50.26	55.9	54.87	54.37
2	54.98	69.78	62.93	60.23
3	61.03	75.98	67.4	63.45
4	68.9	83.56	76.79	78.98
5	79.97	89.91	83.59	86.73
6	84.78	93.45	89.99	90.17
7	90.83	97.99	94.98	95.68
8	95.98	100.2		99.9
9	99.58			100.09

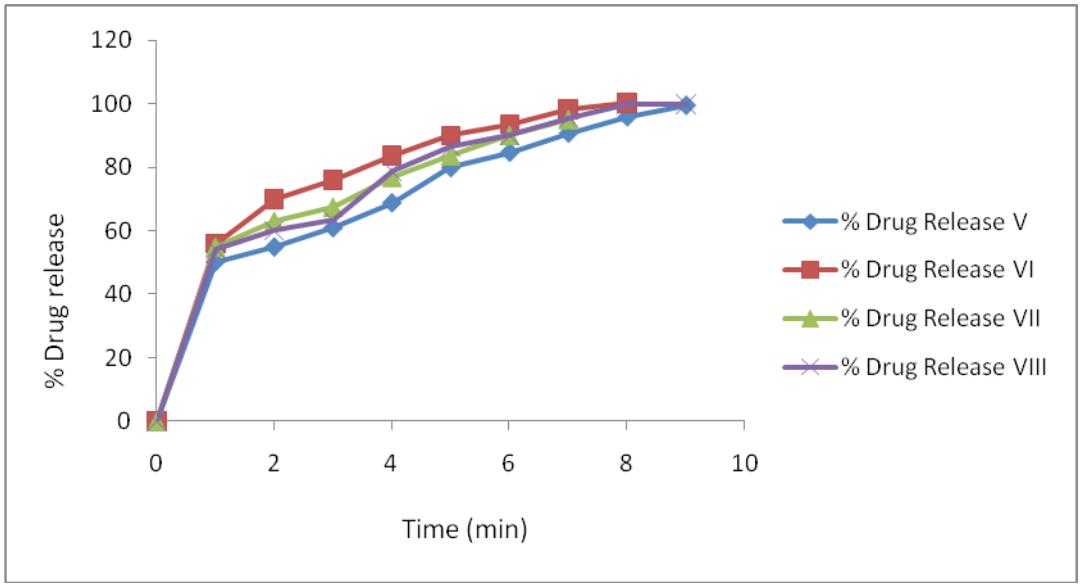


Fig.7.17: Dissolution Testing of batch V-VIII

From above two graphs it was cleared that Rapid increase in dissolution of nifedipine with increase in KYRON 314 may be attributed to rapid swelling and disintegration of tablet into primary particles. CCS exhibit capillary activity and pronounced hydration, with little tendency of gel formation and disintegrate the tablet rapidly but into larger masses of aggregated particle and later resulting in slow release of drug.

7.6 EVALUATION OF THE FLOATING AND PULSATILE RELEASE TABLET (FPRT):

It was observed that the disintegration time for formulation varied from 10 to 52 second. It was observed that when KYRON T314 was used as disintegrant, tablet was disintegrate within short time due to easy and high swelling ability of KYRON T314 as compared to CCS. It is observed that disintegration time of tablet decreased with increased in concentration of CCS and KYRON T-314. But by disintegration study it was observed that hardness plays important role. For development of pulsatile release study disintegration time must be short to obtain burst effect therefore having less hardness. Hence by observing results it was concluded that batches II and VI were optimized batches which were confirmed by dissolution study.

7..6.1 Pulsatile Release Tablet (PRT)

For this study, the core tablets containing nifedipine (RRT) were compression coated with different powder such as HPMC K4, HPMC E15LV, sodium carboxymethylcellulose, used as outer erodible shell. Dissolution studies were carried

out on combination of polymers as well as on individual polymers. Dissolution studies resulted that batches prepared with combined polymers formed too sticky mass to release the drug when polymers came into contact with dissolution medium. From this it was resulted that combined polymers are not suitable for pulsatile drug delivery system Core tablet containing crosscarmellose sodium was compression-coated with HPMC K4, HPMC E15LV, sodium carboxymethylcellulose and these batches were taken as preliminary batches for the study of individual polymers. The in vitro release profiles of nifedipine from different-coated systems in 0.1 M HCl solution was provided in Figure 7.18,7.19, 7.20.

Table 7.8: Dissolution Testing of batch C1-C3

Time (hrs)	% Drug Released		
	C1	C2	C3
0	0	0	0
1	0	0	0
2	5	3	0
3	10.95	5.67	0
4	25.4	7.45	0
5	38.81	24.87	0
6	49.86	39.66	8.01
7	66.54	50.32	25.03
8	78.24	67.53	43.56
9	96.9	88.27	65.75
10	99.61	94.93	80.55
11		98.88	89.6
12		99.97	95.38
13			98.3
14			99.57
15			99.15
16			99.56

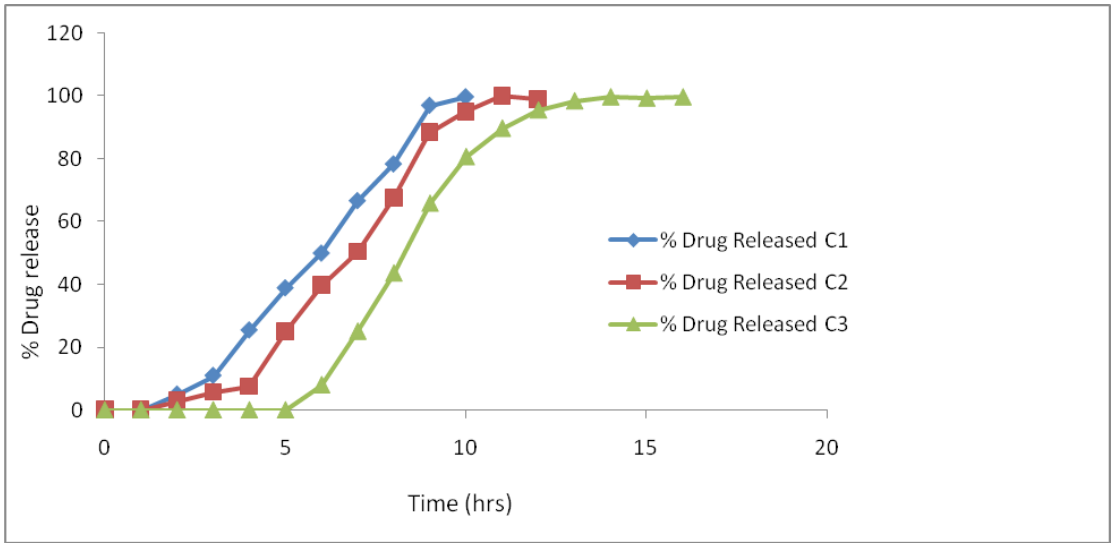


Fig 7.18: In vitro release profiles of Nifedipine from the pulsatile release tablet (PRT) coated with different amount of HPMC K4M.

Table 7.9: Dissolution Testing of batch C4-C6

Time (hrs.)	% Drug Released		
	C4	C5	C6
0	0	0	0
1	0	0	0
2	27.91	0	0
3	52.39	30.87	24.97
4	64.98	51.9	41.74
5	78.49	68.76	65.89
6	90.72	80.95	79.8
7	95.69	91.69	90.98
8	98.19	96.98	96.5
9	99.85	99.81	99.78

10		99.89	99.96
11			99.95

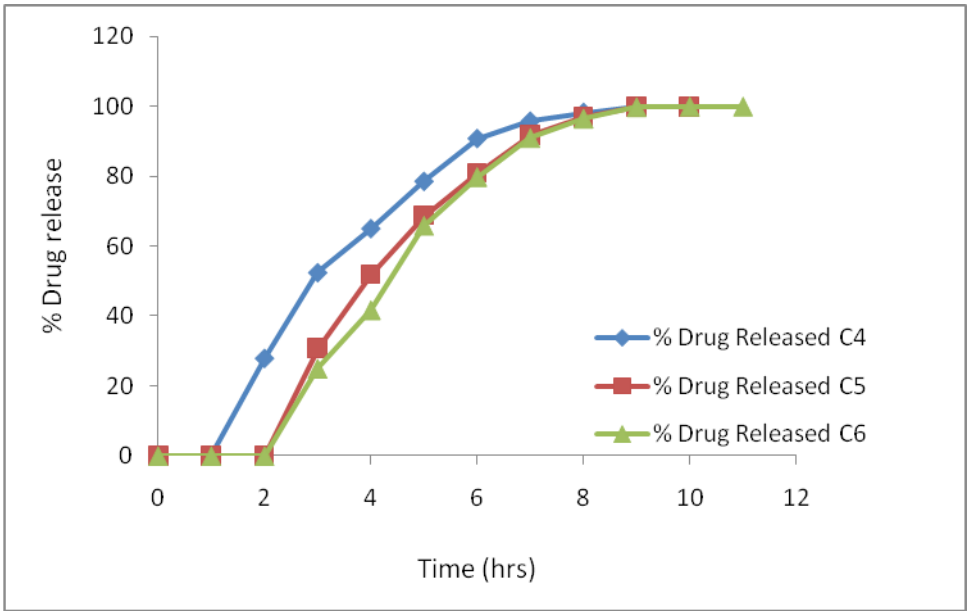


Fig 7.19: In vitro release profiles of Nifedipine from the pulsatile release tablet (PRT) coated with different amount of NaCMC in 0.1 M HCl.

Table 7.10: Dissolution Testing of batch C7-C9

Time (hrs.)	% Drug Released		
	C7	C8	C9
0	0	0	0
1	0	0	0
2	20	0	0
3	27.98	5.98	0
4	51.54	15.9	5.98
5	65.89	29.87	30.98
6	77.97	45.76	50.39
7	83.78	53.21	67.29
8	90.98	68.98	80.96
9	99.55	77.98	86.19
10		85.82	93.98
11		90.89	98.42
12		95.97	99.88
13		99.2	99.96

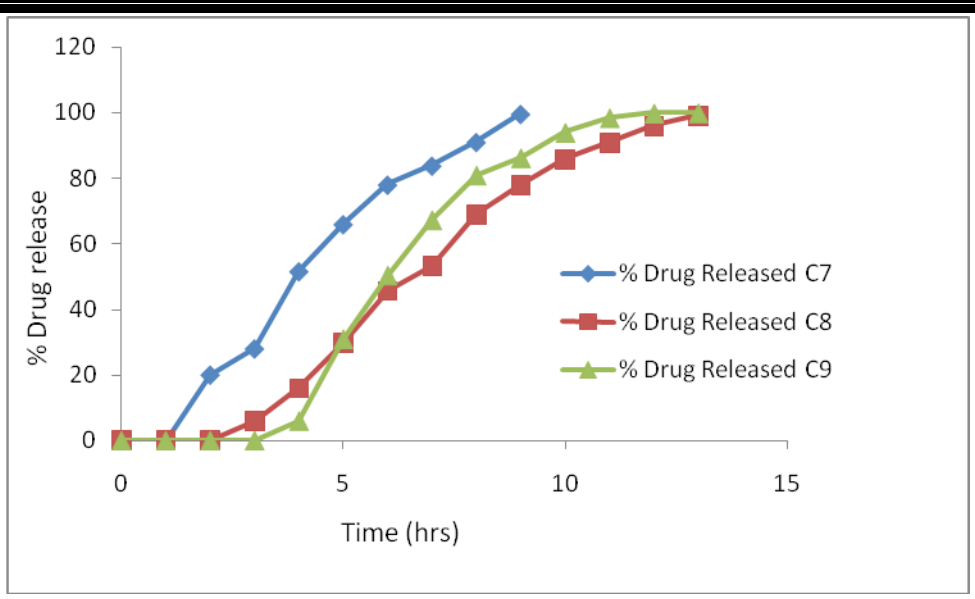


Fig 7.20: In vitro release profiles of Nifedipine from the pulsatile release tablet (PRT) coated with different amount of HPMC E15LV.

Fig 7.18 shows that HPMC K4M gives the lag time of 4 hours then follow the sigmoidal release pattern with 100% drug release at 10th hour. As the concentration of the HPMC K4 coating increases from 140 to 180 mg the lag time extended to 5 hours and then follow the delayed release profile with the 100 % drug release at the 17th to 18th hour From Fig 7.19, it was observed that carboxymethylcellulose sodium (NaCMC) shows the lag time of 2 hours, resulting in rapid and complete drug release at 10th hour. But these tablet did not maintain its shape throughout dissolution process which might be concluded that such tablet cannot be floated for longer period of the time. Due to this reason tablet (PRT) of Carboxymethylcellulose sodium (NaCMC) was not studied further.From fig 7.20 it was observed that HPMC E15LV shows the lag time of 3 hours then follow the sigmoidal release pattern with 100% drug release at 9th hour. As the concentration of the HPMC E15LV coating increases from 240 to 290 mg the lag time extended to 4.5 hours and then follow the delayed release profile with the 100 % drug release at the 12th to 14th hour.From above discussion it was cleared that carboxymethylcellulose sodium (NaCMC) cannot be used to develop a successful pulsatile drug delivery system as it cannot give sufficient lag time and is unable to maintain its shape. Other two polymers can be used to develop effective pulsatile drug delivery system. But these two polymers were giving delayed release pattern after sufficient lag time instead of giving pulsatile release pattern(complete and rapid drug release at once).This may be due to the effect of superdisintegrants

(crosscarmellose sodium). Due to the insufficient swelling of crosscarmellose sodium, it could not give burst release required for complete drug release. Hence these two polymers were further studied by using KYRON T 314 as superdisintegrant in core tablet. Different batches of pulsatile release tablet of HPMC K4M and HPMC E15LV were prepared using KYRON T 314 in core tablet. Fig 7.21, 7.22 shows drug release pattern of batches K1-K6. By studying dissolution profile it was observed that batch K6(290mg) was optimized batch. As the coated tablet was placed in the aqueous medium, it was observed that the hydrophilic polymeric layer started erosion, which underwent progressive modification in terms of thickness and consistency. In the second phase of the dissolution procedure, the coating layer gradually starts to erode up to a limiting thickness. After this stage, a rupture of the shell was observed under the pressure applied by the swelling of the core tablet and Nifedipine released. This pressure was high due to high swelling property of KYRON T314 and which resulted in burst effect along with complete and rapid drug release. In case of other batches i.e K1, K2, K4 and K5 amount of coating polymer was too less to achieve desired lag time. Due to high swelling of inner core tablet coating of K1, K2, K4 and K5 formulations could not maintain too long and result in complete drug release within short time. All of this process corresponded to a lag time capable of exhibiting a pulsatile release of the drug. The profiles relevant to the coated tablet showed that a lag phase was followed by the quickly delivery of the active principle. The delay duration clearly depended on the kind and amount of hydrophilic polymer as which was applied on the core. Invitro the lag time of the tablet coated with 290-mg HPMC E15LV was 4.1±0.2 h and given burst with 96.88% and after this the % drug release remains constant due to non maintenance of sink condition.

Table 7.11: Dissolution Testing of batch K1-K3

Time (hrs.)	% Drug Released		
	K1	K2	K3
0	0	0	0
1	0	0	0
2	20	0	0
3	27.98	5.98	0
4	51.54	15.9	5.98
5	65.89	29.87	30.98
6	77.97	45.76	50.39
7	83.78	53.21	67.29
8	90.98	68.98	80.96
9	99.55	77.98	86.19
10		85.82	93.98
11		90.89	98.42
12		95.97	99.88
13		99.2	99.96

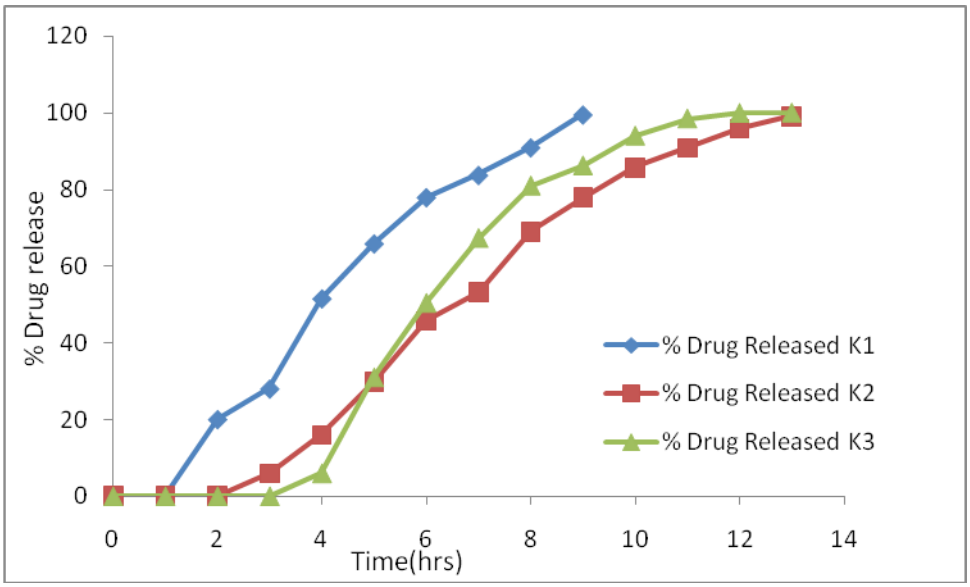


Fig 7.21: In vitro release profiles of Nifedipine from the pulsatile release tablet (PRT) coated with different amount of HPMC K4M+Core tablet containing KYRON T 314.

Table 7.12: Dissolution Testing of batch K4-K6

Time (hrs.)	% Drug Released		
	K4	K5	K6
0	0	0	0
1	0	0	0
2	15.98	3.98	0
3	43.78	39.98	0
4	54.89	59.79	0
5	63.79	71.98	54.98
6	76.89	80.98	74.89
7	87.99	88.93	87.89
8	95.92	94.99	94.98
9	99.89	99.99	98.99
10		100.09	99.98
11		99.89	100.04
12		100.05	99.97
13		100.03	100.06
14		99.99	100.09

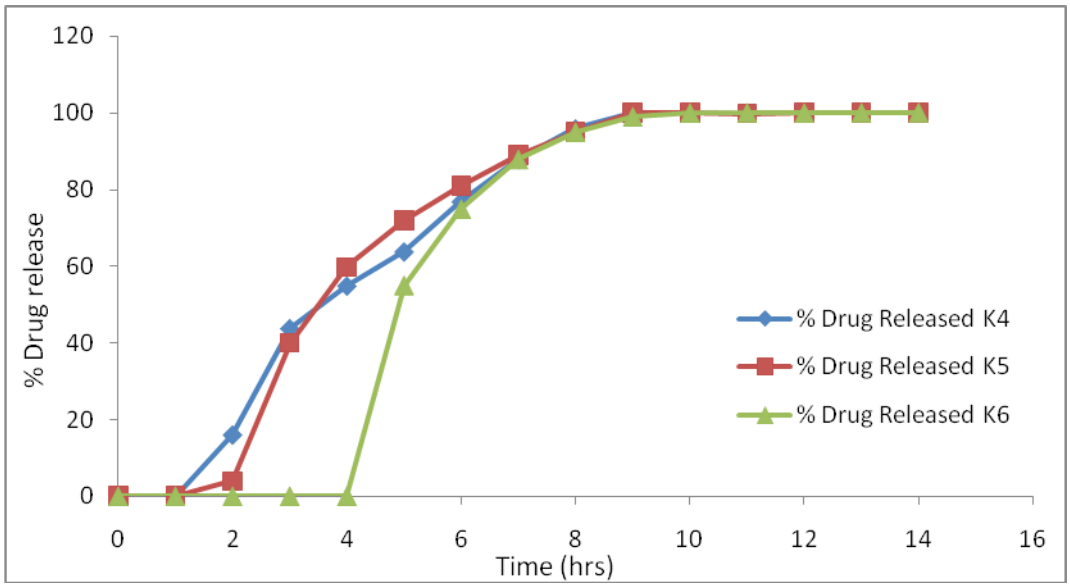


Fig 7.22: In vitro release profiles of Nifedipine from the pulsatile release tablet (PRT) coated with different amount of HPMC E15LV+Core tablet containing KYRON T 314

7.6.2 In Vitro Buoyancy Determination

Table no:13 Onset of time for floating of various formulations

Formulation	Onset of time for floating
F1	Greater than 1 hr
F2	Formulation showed no floating
F3	Remaining floating was no more than 3 h
F4	float completely within 1 min and remained floating over a period of 12 h
F5	Greater than 15 min

Floating behavior of tablet depends on added fillers in buoyant layer. Tablets containing lactose floated earlier than tablets prepared with the inorganic filler dibasic calcium phosphate. This could be explained by the different densities, lactose containing tablet had the lowest density (1.0 g/cm^{3}at a hardness of 4.3 Kg/cm^2), whereas the dibasic calcium phosphate tablet had a much higher density (1.9 g/cm^3 at a hardness of 5.2 Kg/cm^2). In addition, lactose has a higher water solubility, resulting in faster water uptake of medium into tablet. Microcrystalline cellulose, an insoluble filler with high water uptake and disintegration capability, resulted in disintegration of tablet.CO_2 did not accumulate in buoyant layer of tablet and escaped through the disintegrated tablet, floating was therefore not achieved. Based on these results, lactose was identified as the filler of choice and used for further investigation.

F4 formulation was used for further investigation.

7.7 SWELLING INDEX DETERMINATION

Tablet containing HPMC K4M showed high swelling index as compared to HPMC E15LV and NaCMC which might be due to hydration property of HPMC K4M. NaCMC showed swelling property but after some time tablet could not maintain its shape and integrity (Eq 6.1) HPMC K4M and HPMC E15LV showed constant increase in swelling index up to 10 h. (Fig 7.23)

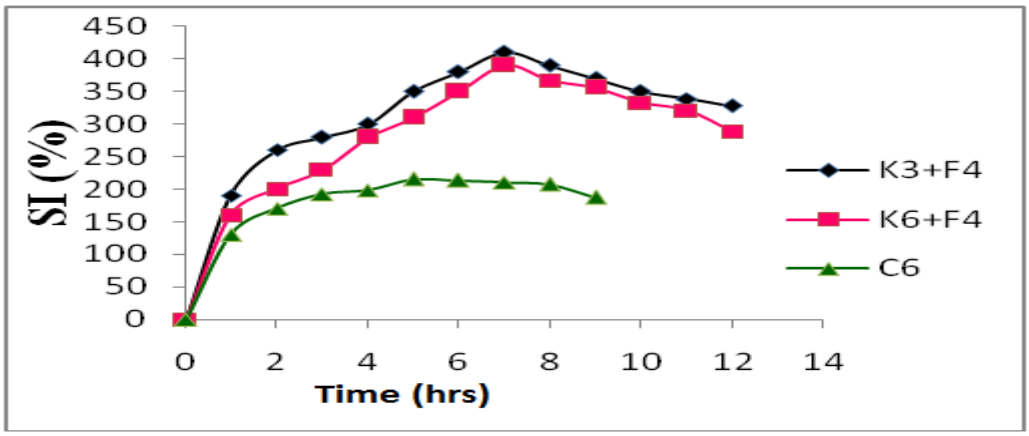


Fig 7.23: Swelling index of tablets of K3+F4, K6+F4 and C6

7.8 FLOATING AND PULSATILE RELEASE TABLET (FPRT)

The FPRT was manufactured as described above and consisted of the buoyant layer F4 (Table 6.8) combined with a PRT containing 20 mg Nifedipine core tablet compression- coated with 290 mg of HPMC E15LV (Formulation K6).

Table 7.14: Dissolution testing of batch K6+F4

Time (hrs.)	% Drug Released
0	0
1	0
2	0
3	0
4	11.09
5	54.98
6	74.89
7	87.89
8	94.98
9	98.99
10	99.98
11	100.04
12	99.97
13	100.06
14	100.09

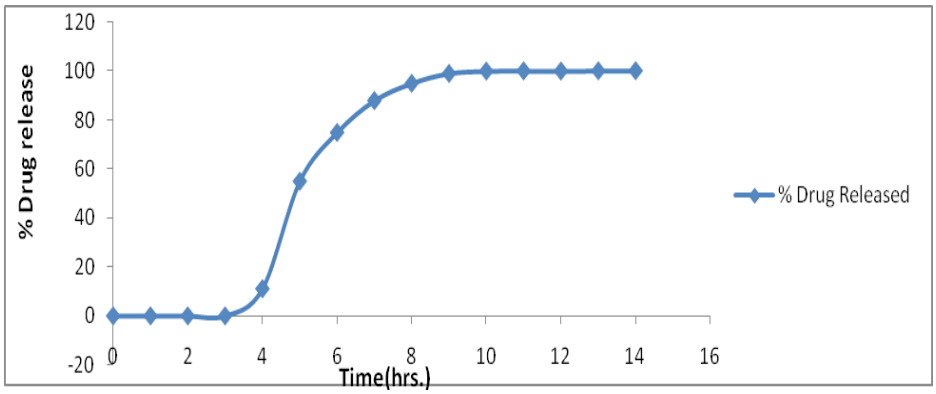


Fig. 7.24: In vitro release profiles of Nifedipine from the floating–pulsatile release tablet (FPRT) Of batch K6+F4

Evaluation Of Floating and Pulsatile Release Tablet:

Only FPRT tablets of optimized batch (K6+F4) were evaluated for friability test, hardness test and drug content. In formulation, the hardness test indicated good mechanical strength. Hardness was ranged from 3.8 to 4.0 Kg/cm^2. Friability was ranged from 0.5 to 0.56. Friability is less than 1% which indicated that tablets had good mechanical resistance. Drug content was found to be high (>99.23). It was ranged from 99.32 to 99.45 and uniform in all tablet formulations. An ultraviolet (UV) spectrophotometric method was given at 236 nm and method obeys Beer's law in concentration range 5 to 50 µg/ml, with good correlation coefficient (0.9997).

Table 7.15: Evaluation Of Floating and Pulsatile Release Tablet

Sr no.	Formulations	Hardness (Kg/cm^2) Friability (%)	Drug content (%)	
1	K6+ F4	3.8	0.43±0.11	99.45

7.10 STABILITY TESTING OF THE BEST FORMULATION

According to the result of dissolution testing, the two batches were selected for the stability studies K6+F4 out of the total formulation batches.Studies were carried out as ICH guidelines

RESULTS OF STABILITY STUDIES FOR BATCH NO. K6+F4:

Sample at 30 C (+/-2 C) and 65% RH (+/-5%) condition

Table no: 7.16: Results of stability studies for batch no. K6+F4.Sample at 30 C (+/-2) and 65% RH (+/-5%) condition

Tests	Initial	7 days	14 days	21 days	1 month	2 month	3 month
Stability out date	2/10/11	9/10/11	16/10/11	23/10/11	30/10/11	30/11/11	30/12/11
Appearance	white colour	white colour	white colour	white colour	white colour	white colour	white colour
LOD (%)	0.423	0.458	0.419	0.449	0.431	0.474	0.487
Assay (%)	99.73	99.65	99.57	98.48	99.33	99.26	99.14
Tests	Initial	7 days	14 days	21 days	1 month	2 month	3 month
Stability out date	2/10/11	9/10/11	16/10/11	23/10/11	30/10/11	30/11/11	30/12/11
Dissolution study Time (hr)	**% Drug Release**						
0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0
4	5.24	7.54	5.89	4.66	4.36	7.32	5.89
5	13.86	14.24	12.54	11.35	14.38	12.54	13.33
6	33.67	48.3	37.78	37.37	58.3	34.06	37.38
7	54.73	55.52	48.96	57.36	65.52	52.32	57.32
8	69.99	76.28	65.55	65.29	76.28	68.53	65.27
9	87.77	92.92	76.98	77.26	92.92	89.70	77.26
10	96.35	98.59	86.42	85.24	98.59	95.93	96.44
11	98.25	96.96	98.79	98.76	96.96	99.80	98.76
12	99.38	99.18	99.88	100.66	99.18	100.19	100.07
13	98.99	100.89	99.86	99.41	100.89	100.54	99.50
14	98.35	98.57	98.98	98.57	98.57	99.78	98.56
15	99.57	99.67	100.39	98.99	99.67	98.44	98.98

Fig.7.25: LOD of stability batch K6+ F4, 30^{0}C±2 and 65% RH ±5%

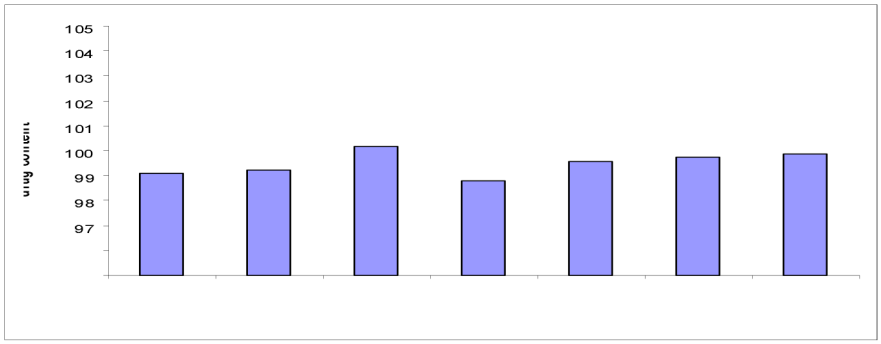


Fig.7.26: % drug content of stability batch K6+F4, 30^{0}C±2 and 65% RH±5%

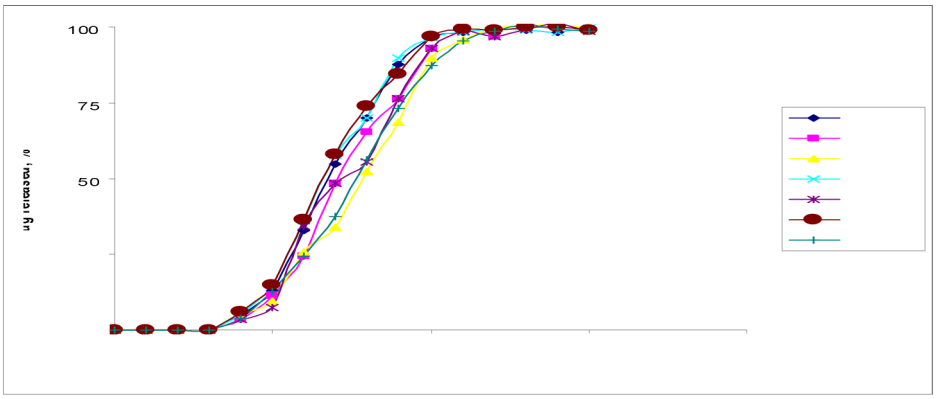


Fig.7.27: Dissolution testing of stability batch K6+F4, Sample at 30^{0}C ±2 and 65% RH ±5%

Table no :17 Hardness, Friability, Disintegration Time of batch K6+F4 at 30^{0}C±2 /65%RH ±5%

Days	Hardness Kg/cm^2	Friability (%)	Disintegration Time(S)
Initial	3.5	0.65±0.12	33
7 days	3.4	0.66±0.14	19
14 days	3.6	0.64±0.11	30
21 days	3.7	0.63±0.11	23
1 month	3.6	0.63±0.14	35
2 month	3.5	0.67±0.13	19
3 month	3.4	0.68±0.16	48

Table no: 7.18. Results of stability studies for batch no. K6+F4.Sample at 40^{0}C (+/-2 C) and 75% RH (+/-5%) condition

Tests	Initial	7 days	14 days	21 days	1 month	2 month	3 month
Stability out date	2/10/11	9/10/11	16/10/11	23/10/11	30/10/11	30/11/11	30/12/11
Appearance	white colour	white colour	white colour	white colour	white colour	white colour	white colour
LOD (%)	0.443	0.468	0.428	0.473	0.459	0.493	0.499
Assay (%)	99.11	99.23	100.17	98.28	99.56	99.72	99.86
Tests	Initial	7 days	14 days	21 days	1 month	2 month	3 month
Stability out date	2/10/11	9/10/11	16/10/11	23/10/11	30/10/11	30/11/11	30/12/11
Dissolution study Time (hr)	**% Drug Release**						
0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0
4	5	2.37	5.12	4.56	3.46	2.14	1.03
5	13	4.36	9.43	7.32	7.54	5.89	4.66
6	33	14.38	25.86	12.54	14.24	12.54	11.35
7	54.73	58.3	34.06	34.06	48.3	37.78	37.37
8	69.99	65.52	52.32	52.32	55.52	48.96	57.36
9	87.77	76.28	68.53	68.53	76.28	65.55	65.29
10	96.35	92.92	89.70	89.70	92.92	76.98	77.26
11	98.25	98.59	95.93	95.93	98.59	86.42	85.24
12	99.38	96.96	99.80	99.80	96.96	98.79	98.76
13	98.99	99.18	100.19	100.19	99.18	99.88	100.66
14	98.35	100.89	100.54	100.54	100.89	99.86	99.41
15	99.57	98.57	99.78	99.78	98.57	98.98	98.57

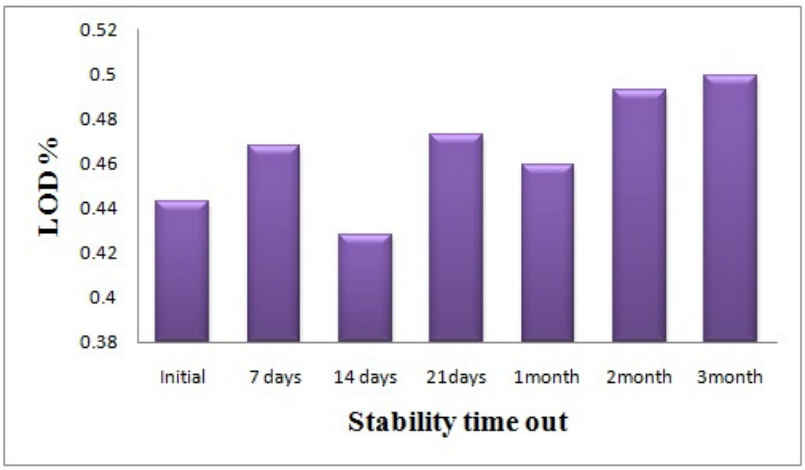


Fig.7.28: LOD of stability batch K6+F4, Sample at 40^{0}C (+/-2 C) and 75% RH (+/-5%)

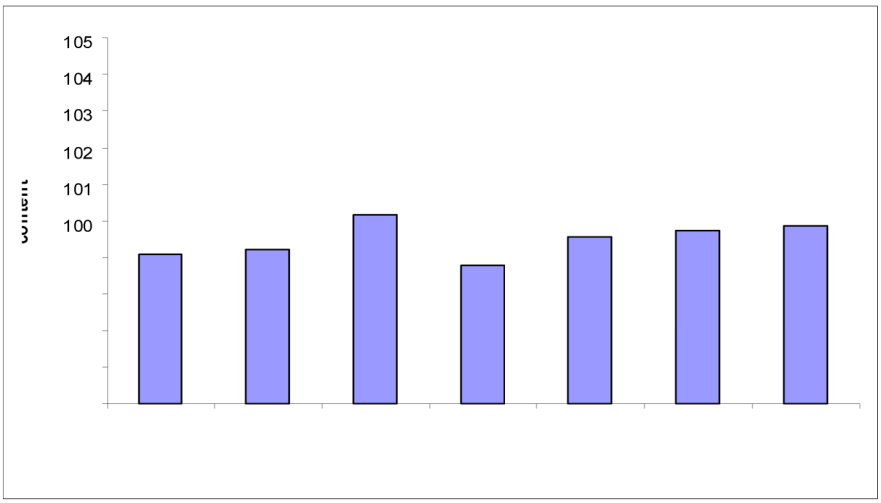


Fig.7.29: % drug content of stability batch K6+F4, Sample at 40^{0}C (+/-2 C) and 75% RH (+/-5%) condition

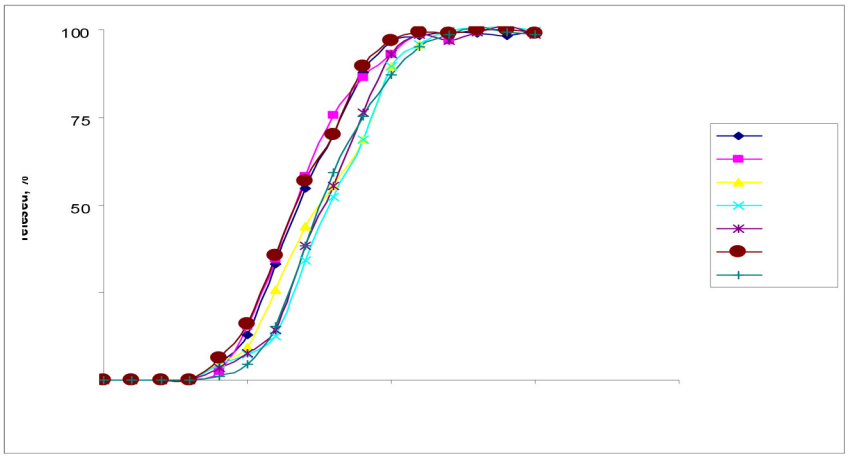


Fig.7.30: Dissolution testing of stability batch K6+F4, Sample at 40^{0}C (+/-2 C) and 75% RH (+/-5%) condition

Table no: 19 Hardness, Friability, Disintegration Time(S) of batch K6+F4 at 40^{0}C±2 /75%RH ±5%.

Days	Hardness Kg/cm^2	Friability (%)	Disintegration Time(S)
Initial	3.7 0.61±0.11	35	
7 days	3.6	0.67±0.15	21
14 days	3.7	0.65±0.11	34
21 days	3.5	0.63±0.14	26
1 month	3.6	0.60±0.15	30
2 month	3.6	0.66±0.13	17
3 month	3.8	0.61±0.16	45

For Floating pulsatile release tablet of nifedipine optimized batch K6+F4 from Table 7.12-7.13 , it was seen that there are no significant changes in drug release profile for the batches stored at 30^0C (+/-2 C) and 65% RH (+/-5%) and 40^0 C (+/-2 C) and 75% RH (+/-5%) when compared with initial batch.

From the stability data it can be concluded that there were no changes in any parameter tested in formulation, so the optimized batch K6+F4 are said to be stable.

7.9 KINETICS OF DRUG RELEASE

Table No 7.20 Kinetics of Drug Release Study of K6+F4

Batch No	Zero order (R^2)	Firstorder (R^2)	Higuchis P lot (R^2)	Hxison Crowell (R^2)	Korsmeyer pepps		
					(R^2)	(n)	Order release
K6+F4	0.7962	0.6541	0.9291	o.8355	0.9997	0.5854	Non - Fickian

8. SUMMARY

The main objective of the study was to develop a Time-Controlled release formulation based on a Floating Pulsatile Drug Delivery System. The intention is that the formulation should be administered in the evening at 22:00 in treating diseases in which symptoms are experienced in the early morning hours (from 04:00 to 06:00).

The core tablets prepared with different superdisintegrants were subjected for evaluation of the in-vitro disintegration time and it was observed that the time for formulation varied from 10 to 52 second. It will observed that when KYRON T314 was used as disintegrant, tablet was disintegrate within short time due to easy and high swelling ability of KYRON T314 as compared to CCS. It is observed that disintegration time of tablet decreased with increased concentration of CCS and KYRON T-314. But by disintegration study it was observed that hardness plays important role. For development of pulsatile release study disintegration time must be short to obtain burst effect therefore having less hardness. Hence by observing results it was concluded that batches II and VI were optimized batches which was confirmed by dissolution study.

Core tablet containing crosscarmellose sodium was compression-coated with HPMC K4, HPMC E15LV, sodium carboxymethylcellulose (C1-C9) and these batches were taken as preliminary batches for the study of individual polymers.

HPMC K4M (Batch C1-C3) gives the lag time of 4 hours then follow the sigmoidal release pattern with 100% drug release at 10^{th} hour. As the concentration of the HPMC K4 coating increases from 140 to 180 mg the lag time extended to 5 hours and then follow the delayed release profile with the 100 % drug release at the 17^{th} to 18^{th} hour.

From dissolution study it was observed that carboxymethylcellulose sodium (NaCMC) shows the lag time of 2 hours, resulting in rapid and complete drug release at 10^{th} hour (Batch C4-C6). But these tablet did not maintain its shape throughout dissolution process which might be concluded that such tablet cannot be floated for longer period of the time. Due to this reason tablet (PRT) of Carboxymethylcellulose sodium (NaCMC) was not studied further.

HPMC E15LV (Batch C7-C9) shows the lag time of 3 hours then follow the sigmoidal release pattern with 100% drug release at 9^{th} hour. As the concentration of the HPMC E15LV coating increases from 240 to 290 mg the lag time extended to 4.5

hours and then follow the delayed release profile with the 100 % drug release at the 12^{th} to 14^{th} hour.

Different batches of pulsatile release tablet of HPMC K4M and HPMC E15LV were prepared using KYRON T 314 in core tablet (Batch K1-Batch K6). By studying dissolution profile it was observed that batch K6(290mg) was optimized batch.

The behavior of the tablet is determined by using USP dissolution apparatus-II in 500 ml of 0.1 N HCl. Behavior of tablet depends on added fillers (Dicalcium phosphate, microcrystalline cellulose and lactose) in buoyant layer. F4 formulation was found to float completely within 1 min and remained floating over a period of 12 h. The PRT was manufactured as described above and consisted of the buoyant layer F4 (Table 4) combined with a PRT containing 25 mg Nifedipine core tablet compression- coated with 290 mg of HPMC E15LV (Formulation K6). Lag time of PRT coated with 290-mg HPMC E15LV was 4.1±0.2 h which was considered as suitable lag time for Nifedipine preventing the time-related occurrence of ischemic.

For pulsatile release tablet of Nifedipine optimized batch K6+F4 was selected for stability testing, it was seen that there are no significant changes in drug release profile for the batches stored at 30^0C (+/-2 C) and 65% RH (+/-5%) and 40^0 C (+/-2 C) and 75% RH (+/-5%) when compared with initial batch.Optimized batch K6+f4 was selected for kinetic study. The value of correlation coefficient is 0.9997 which most near to 1 and slope was found to be 0.584.Hence it was concluded that the optimized batch was found to follw korsmeyer and peppas model.So it is concluded that formulation release the drug by diffusion and erosion method.

CONCLUSION

The core containing KYRON T-314 disintegrate the tablet within short time due to easy and high swelling ability of KYRON T-314 as compared to CCS The PRT containing the buoyant material, such as HPMC K100M, $NaHCO_3$,and citric acid achieved a satisfactory buoyant force in vitro, whereas the floating onset time was less than 1 min. The pulsatile releasing mechanism of PRT is based on the exploitation of the peculiar interaction between hydrophilic polymeric coating and the aqueous gastrointestinal fluids.

The in vitro release profiles of Nifedipine from PRT prepared using HPMC E15LV as retarding polymer are characterized by a predetermined lag time (4.1±0.2 h for K6+F4), the duration of which depends on the kind and amount of the polymeric layer applied on the cores as well as type of superdisintegrant in core tablet. The developed system offers a simple and novel technique for pulse release of drugs. From the results it is concluded that the PRT we prepared could achieve a rapid release after lag time of 4±0.2h with the relatively low variability. The drug release profile of optimized batch K6+F4 was found to be follow korsmeyer and peppas model. So it is concluded that formulation release the drug by diffusion and erosion method.

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